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# The Use of Gases in Flow Synthesis

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**ABSTRACT:** This review will highlight the potential benefits that can be leveraged by using flow chemistry to allow gases to be used in research in a safer and more efficient way. An overview of the different approaches used to introduce gases into flow reactors is presented along with a synopsis of the different gaseous reactions classes already successfully translated into flow.

## INTRODUCTION

The use of toxic and dangerous gases is highly restricted and controlled in modern synthetic laboratories. Increased safety considerations, including precautionary limitations on their use at scale, are often mandated for gas processing operations. Understandably, for something as ethereal as a gas, which cannot be easily contained, leakages are very difficult to prevent when conventional synthetic equipment is used. Consequently, dedicated high-pressure facility rooms are normally built specifically to enable access to gas-based transformations. Pressurised gas reactions are normally continually monitored for leakage using specialized gas and/or pressure detectors, with the personnel using such facilities having to undergo specialized training. Furthermore, restrictions on the scales of high-pressure reactions are also put in place to mitigate risks, making the scale up of these reactions challenging.

## ALTERNATIVE APPROACHES

The use of gas surrogates has been developed to circumvent the direct use of certain gases, with the *in situ* liberation of the required gas being the most common method. Several carbon monoxide precursors exist, such as those derived from aldehydes,<sup>1</sup> formyl saccharine,<sup>2</sup> and various metal carbonyls, such as Ni(CO)<sub>4</sub>,<sup>3</sup> W(CO)<sub>6</sub>,<sup>4</sup> and Mo(CO)<sub>6</sub>.<sup>5</sup> Similarly, the use of transfer hydrogenation is often applied as a substitute for gaseous hydrogen, which can be delivered through a donor such as formic acid via a metal complex (e.g., Ru),<sup>6</sup> often in association with diamine or phosphine ligands. It is also possible to use metal-free hydrogen gas substitutes such as Hantzsch esters often promoted by the addition of an auxiliary organocatalyst.<sup>7</sup> Additional gas substitutes for less common species have also been developed such as Selectfluor (which acts as a F donor)<sup>8</sup> and DABSO as a gaseous sulfur dioxide substitute.<sup>9</sup> Even though these gas substitutes are useful for small scale chemistry, they often tend to be either too toxic,<sup>10</sup> atom inefficient, or too expensive to be used at larger scales.

## APPLICATION OF GASES

One of the main limiting factors when pursuing a transformation using a gaseous component is establishing the required stoichiometry by solubilizing sufficient quantities of the gas into the reaction media. The low solubility of certain gases, like carbon monoxide (Table 1),<sup>11</sup> often deems that high-pressures are required, with the concentration of the dissolved gas also showing a rapid decrease with an increase in

**Table 1. Solubility of Carbon Monoxide in Selected Solvents at 25 °C<sup>11</sup>**

solvent	molar volume	solubility C <sup>a</sup>
<i>n</i> -heptane	146.46	11.71 × 10 <sup>-3</sup>
cyclohexane	108.75	9.12 × 10 <sup>-3</sup>
methylcyclohexane	128.35	9.68 × 10 <sup>-3</sup>
toluene	106.86	7.59 × 10 <sup>-3</sup>
perfluoroheptane	227.33	17.11 × 10 <sup>-3</sup>
perfluorobenzene	115.79	1.35 × 10 <sup>-3</sup>
chloroform	80.94	7.94 × 10 <sup>-3</sup>
acetone	74.01	10.44 × 10 <sup>-3</sup>
methanol	40.73	9.24 × 10 <sup>-3</sup>
ethanol	58.68	8.26 × 10 <sup>-3</sup>
<i>n</i> -propanol <sup>b</sup>	74.79	7.36 × 10 <sup>-3</sup>
<i>i</i> -propanol	76.55	7.89 × 10 <sup>-3</sup>
isobutanol	92.88	7.03 × 10 <sup>-3</sup>
dimethylformamide <sup>b</sup>	77.04	1.82 × 10 <sup>-3</sup>
water	18.07	0.95 × 10 <sup>-3</sup>

<sup>a</sup>Concentration in moles per liter at 1 atm partial pressure of carbon monoxide. <sup>b</sup>Measurements taken at 20 °C.

temperature, especially when the boiling point of the solvent is approached. Thus, following Henry's law, when the reaction temperature is elevated, an increase in pressure is required to maintain the same concentration of dissolved gas.

Continuous flow technology can provide many advantages over traditional batch synthesis.<sup>12</sup> First, the high heat and mass transfer rates that are possible when using small channelled fluidic systems enable reactions to be performed under a wider range of conditions, many of which are not accessible within conventional batch reactors. In the case of gas–liquid reactions, a high interfacial area (*a*) is essential for an efficient mass transfer rate. Batch reactions performed in a traditional round-bottomed flask have much lower interfacial areas, and this decreases with an increase in the size of the flask (Figure 1). Note that when the reaction is stirred, the vortex formed increases the interfacial area, which also depends on the speed of mixing. Table 2 shows some published interfacial areas for

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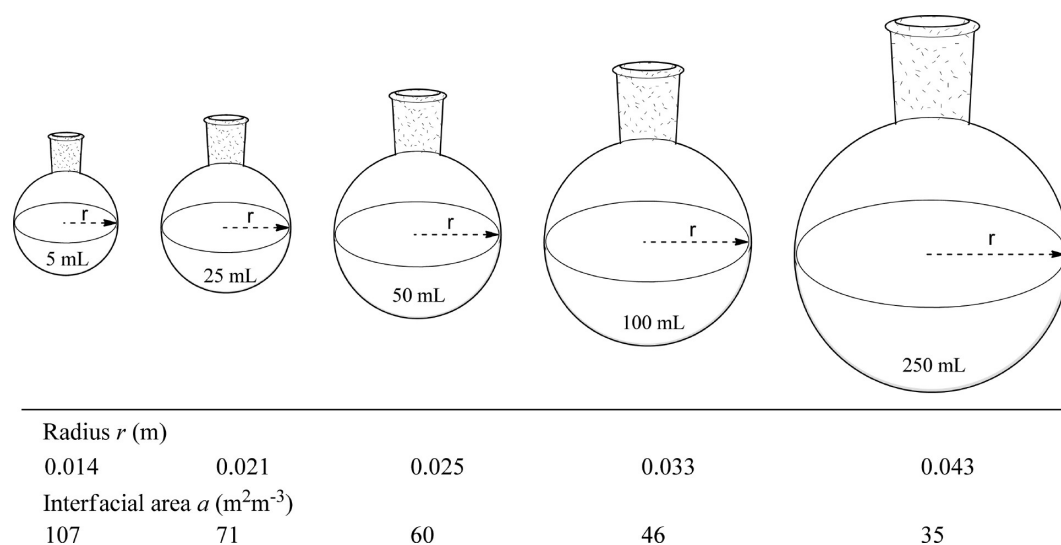


Figure 1. Qualitative measure of interfacial area ( $a$ ) for typical round-bottom flasks when the liquid is static.

Table 2. Published Interfacial Area for Different Gas–Liquid Contactors<sup>13</sup>

type of contactor	$a$ ( $\text{m}^2 \text{m}^{-3}$ )
bubble columns	50–600
Couette–Taylor flow reactor	200–1200
impinging jet absorbers	90–2050
packed columns, concurrent	10–1700
packed columns, counter current	10–350
spray column	75–170
static mixers	100–1000
stirred tank	100–2000
tube reactors, horizontal and coiled	50–700
tube reactors, vertical	100–2000
gas–liquid microchannel contactor	3400–18 000

different reactors, showing much larger values for certain reactor types, especially microchannel reactors ( $a = 3400$  to  $18\,000 \text{ m}^2 \text{m}^{-3}$ ), with a maximum interfacial value of  $18\,000 \text{ m}^2 \text{m}^{-3}$  for a  $300 \mu\text{m} \times 100 \mu\text{m}$  microchannel.<sup>13</sup>

A significant increase in the interfacial contact area can permit reactions that are not normally feasible under conventional batch synthesis conditions to be promoted in flow. In general, gases are easier to use in flow, as their delivery can be regulated by dosing controlled flow volumes and using the higher internal pressures within the flow system to aid dissolution. Since flow technology also allows for coupling multiple connected reactors, the storing of chemicals is reduced together with shipping costs, as intermediates needed for the desired product can be potentially synthesized and used directly in the next step without the need of isolation. Also, hazardous chemicals, such as pyrophoric or air-sensitive chemicals, are much easier to use without the need for complicated precautions. Scale-up to production levels is potentially easily achieved by replicating the same reactor used for pilot plant experiments via a numbering-up approach or through prolonged running of the same reactor in a continuous manufacture scenario without any redesign in the setup. Both approaches drastically reduce the transition time moving to scale and are thus financially beneficial.

## ■ APPROACHES USED IN MICRO AND MESO GAS–LIQUID FLOW REACTIONS

Microchannel reactors have been extensively used by employing a biphasic flow regime, most commonly segmented flow,

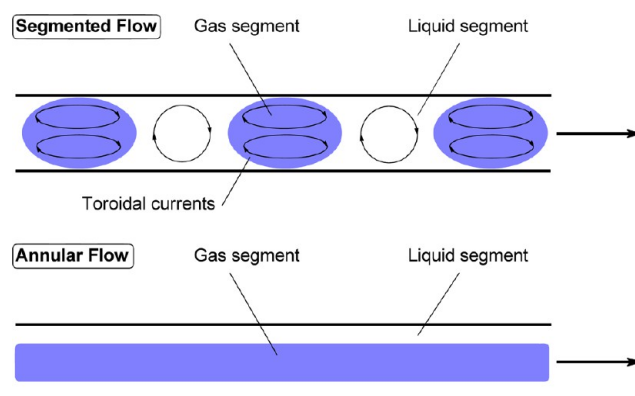


Figure 2. Gas–liquid flow regimes: segmented flow and annular flow.

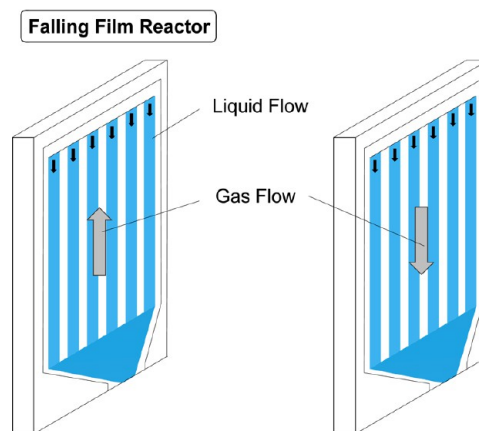
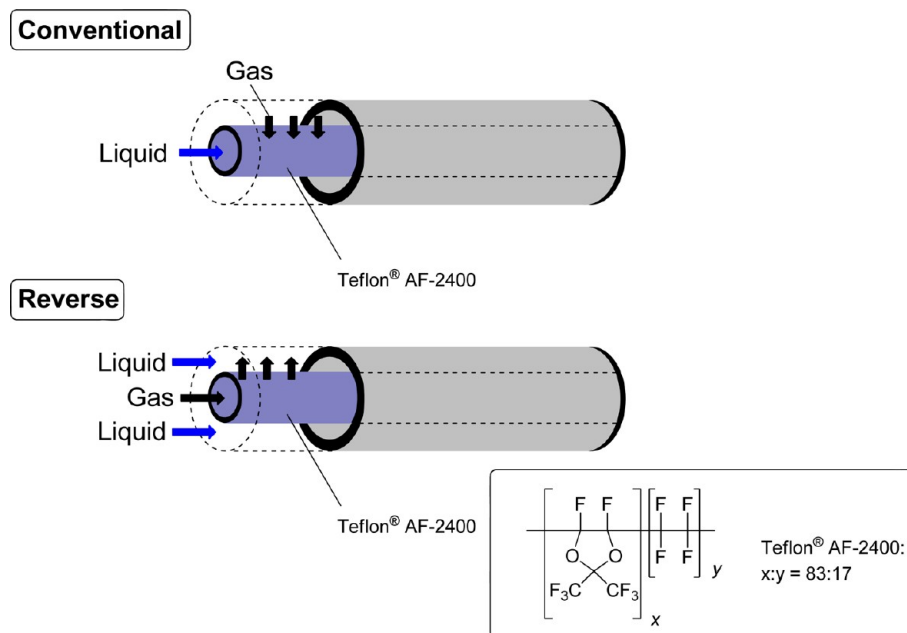
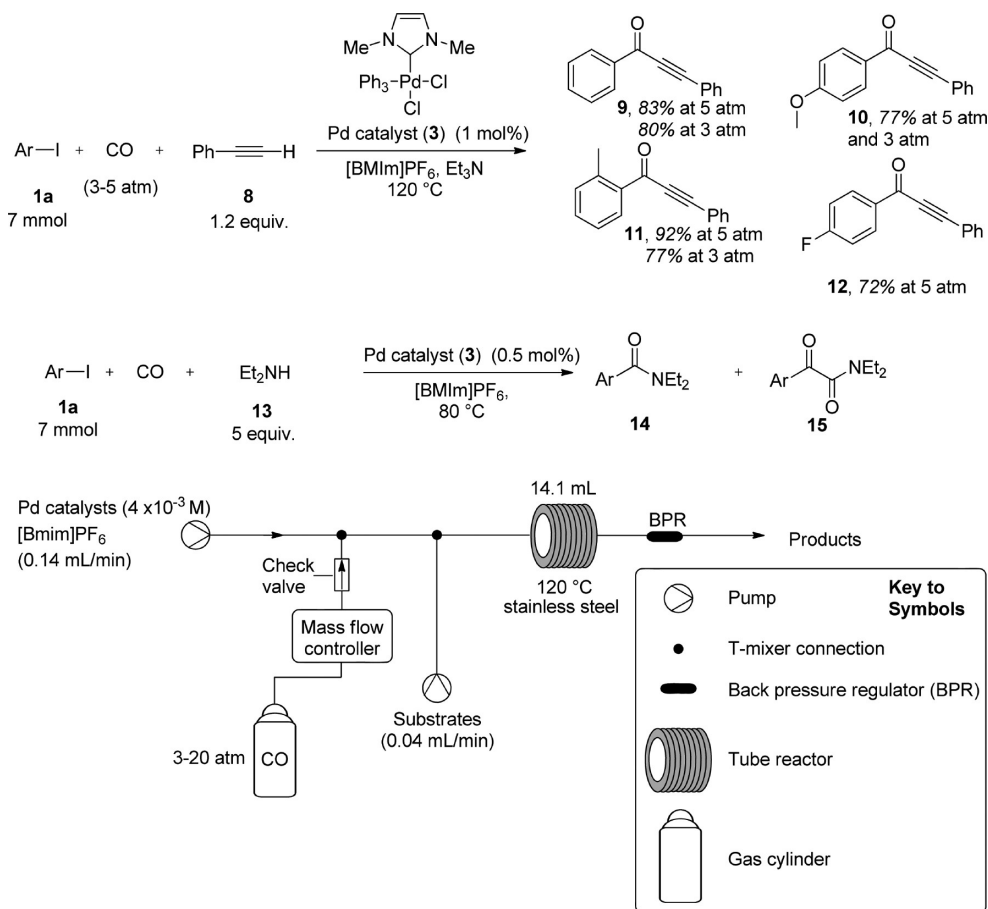


Figure 3. Falling film reactor with liquid flow falling downward and gas flowing either upward (left) or downward (right) above the liquid flow.



**Figure 4.** Tube-in-tube reactors: conventional design with liquid flowing through the inner tube (top) and reverse design with gas flowing through the inner tube (bottom).

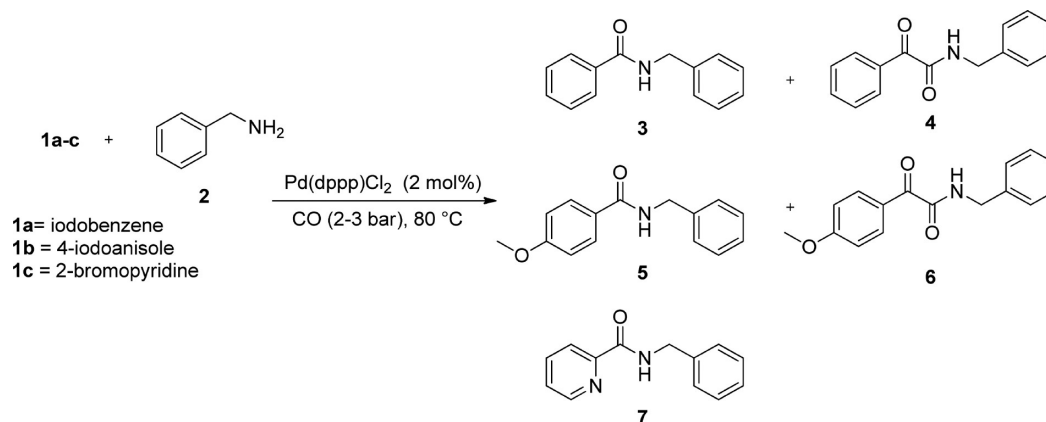
**Scheme 1. Palladium-Catalyzed Carbonylative Coupling of Aryl Iodides and Phenylacetylene in Flow**



where bubbles of a gas are separated by slugs of a liquid (Figure 2). The toroidal currents formed in both the liquid and gas segments enhance the mixing and increase mass transfer.<sup>14</sup> Another approach, which also involves a gas and a liquid stream

concurrently flowing together, is created by the introduction of a fast flowing gas stream injected at high pressures into a slower liquid flow (Figure 2). The velocity of the gas creates an annular flow (pipe flow) with the liquid being pushed against

Table 3. Amino-Carbonylation in Microflow with Benzylamine as the Nucleophile



substrate	residence time (min)	yield of amide (%)	yield of $\alpha$ -ketoamide (%)	total yield (%)
1a	3.75	31	18	49
1a	7.5	37	17	54
1a	15	46	9	55
batch		25	0	25
1b	3.75	10	20	30
1b	7.5	10	19	29
1b	15	12	28	40
batch		11	0	11
1c	3.75	46	0	46
1c	7.5	51	0	51
1c	15	58	0	58
batch		18	0	18

the boundary walls of the microchannels. The thin liquid layer again allows for a high interfacial contact area, with a decrease in the diffusion length.

A further reactor design based upon this same principle is the falling film microreactor, in which the liquid phase flows through microchannels under gravity to form a thin liquid layer.<sup>15</sup> The gas input then flows cocurrently or counter-currently to the liquid (Figure 3).

Mesh microreactors also have been used for gas–liquid flow reactions. This design makes use of a fine metal or ceramic mesh separating the liquid flow in the microchannels. The gas component is passed into the reactor and flows through the mesh to enter the liquid stream.<sup>16</sup> The fine openings in the mesh (average pore size of 76  $\mu\text{m}$ ) allows for an increase in the gas–liquid interfacial contact area, and the small gap separating the mesh and the microchannel allows for a very short diffusion length.

A related approach involves the use of a gas-permeable membrane system that spatially separates the liquid and gas flows by creating a monodirectional barrier. Several such systems have been constructed that make use of this reactor format, employing gas-porous interleaved sheets, wafers, or tubing. As an example, the conventional “tube-in-tube” design reported by the Ley group<sup>17</sup> makes use of an amorphous fluoropolymer Teflon AF-2400 membrane that has high permeability for gases but not liquids.<sup>18</sup> The design enables the formation of microbubbles around the outer walls of the membrane tubing, which are quickly dissolved into the traversing liquid flow (Figure 4). As a consequence of the large surface area and small cross-sectional diameter of the Teflon AF-2400 tubing, gas diffusion across the membrane and into the inertia flow stream is extremely rapid. The Jensen

group studied the diffusion phenomenon of several different configurations of the tube-in-tube design involving the conventional and reengineered reverse designs (Figure 4).<sup>19</sup> The reverse tube-in-tube design, also known as the on-demand design, is capable of being additionally heated to warm the liquid flow while also supplying the gas, whereas the conventional tube-in-tube design can be used only to saturate the liquid flow with a gas at ambient temperature. Despite this limitation, the simple assembly of the conventional tube-in-tube design still makes this setup attractive. It can be easily constructed from commercially available amorphous fluoropolymer Teflon AF-2400 membrane tubing simply inserted into a length of wider bore PTFE tube and connected by the appropriate Swagelok unions. The corresponding reverse tube-in-tube design is now available as a ready-made unit from several leading flow equipment suppliers.

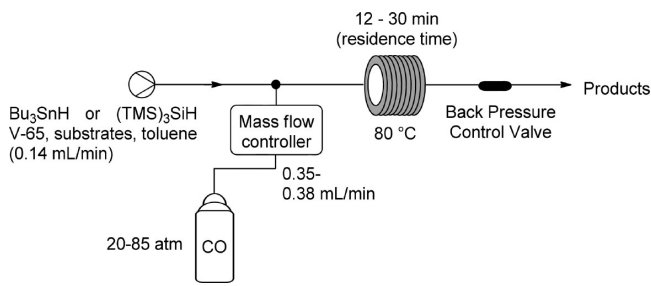
## DIFFERENT GASES USED IN FLOW







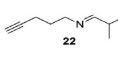
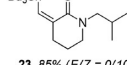

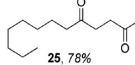

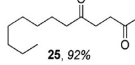

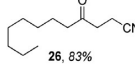
As a consequence of all of the new techniques developed for the easier introduction of gases to flow systems, the area of gas–liquid reactions has become an increasingly popular research topic. Several groups have made substantial progress in overcoming problems normally encountered when gases are used in batch, as we will illustrate in the next sections.

**Carbon Monoxide.** Carbon monoxide is a toxic (poisoning symptoms occur above 50 ppm concentration in air)<sup>10</sup> and highly flammable gas; due to its limited solubility in most organic solvents (Table 1), reactions employing it are most commonly carried out at elevated pressure. This makes the use of carbon monoxide a risk, especially in standard laboratories or when large quantities are needed. However, because it is a synthetically versatile and low-cost building block, chemists



Table 4. Radical Carbonylation in Microflow System



Entry	Substrate	Conditions	Substrate/Yield (%)
1		0.02 M in toluene, Bu <sub>3</sub> SnH (1.2 equiv.), V-65 (10 mol%), CO 83 atm 12 min	 17, 77%
2		0.02 M in toluene, Bu <sub>3</sub> SnH (1.2 equiv.), V-65 (10 mol%), CO 85 atm 12 min	 19, 68%
3		0.02 M in toluene, Bu <sub>3</sub> SnH (1.2 equiv.), V-65 (10 mol%), CO 85 atm 12 min	 21, 86%
4		0.05 M in toluene, Bu <sub>3</sub> SnH (1.1 equiv.), V-65 (10 mol%), CO 79 atm 27 min	 23, 85% (E/Z = 0/100)
5		0.017 M in toluene, Bu <sub>3</sub> SnH (1.5 equiv.), H <sub>2</sub> C=CH-COCH <sub>3</sub> (4 equiv.) V-65 (10 mol%), CO 85 atm 29 min	 25, 78%
6		0.02 M in toluene, (TMS) <sub>3</sub> SiH (1.5 equiv.), H <sub>2</sub> C=CH-COCH <sub>3</sub> (1.2 equiv.) V-65 (30 mol%), CO 20 atm 30 min	 25, 92%
7		0.02 M in toluene, (TMS) <sub>3</sub> SiH (1.5 equiv.), H <sub>2</sub> C=CH-CN (1.2 equiv.) V-65 (30 mol%), CO 20 atm 30 min	 26, 83%

have continued using it despite its associated hazards.<sup>20</sup> Indeed, carbon monoxide is perhaps one of the most used gases, and as such, it is used in several industrial processes such as the Fischer-Tropsch process<sup>21</sup> and alcohol formation through hydroformylation.<sup>22</sup> Carbon monoxide is also routinely used for the conversion of aryl halides and pseudohalides to higher oxidation level groups such as amides, esters, aldehydes, and carboxylic acids (Schemes 1–9 and 16 and Tables 3–5).

The Long group reported one of the first examples of flow carbonylation in 2006 as a safe and scalable way to make simple amides from iodobenzene (**1a**), 4-iodoanisole (**1b**), and 2-bromopyridine (**1c**) with benzyl amine as the substrate. A microfluidic reactor was used to combine the reactants, and a

base and the carbon monoxide were delivered in an annular flow regime.<sup>23</sup> The reactions were compared with existing batch protocols, and, although the yields from the microflow system were only moderate (12–58% yields of amide formed), they were an improvement on those obtained in batch (11–25% yields, Table 3). Of note was the  $\alpha$ -ketoamide byproduct, formed through overcarbonylation, which was also observed under some of the flow reaction conditions.

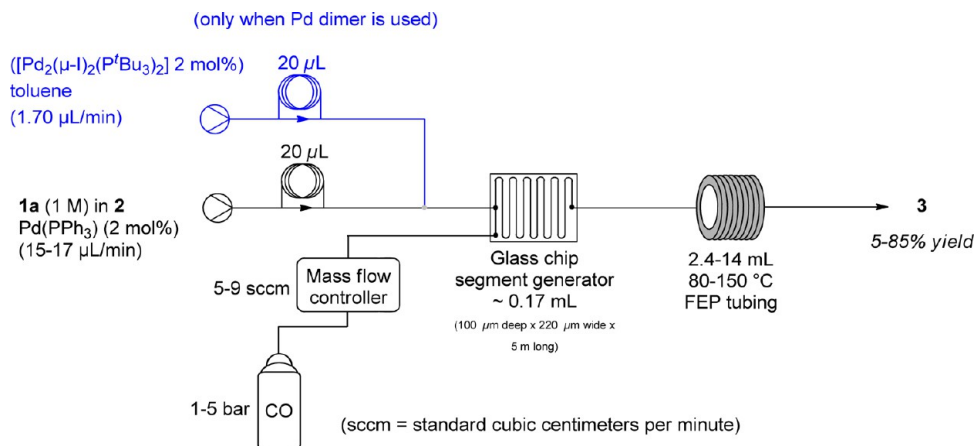
Ryu et al. later published a flow carbonylation protocol for aryl iodides and phenylacetylene in ionic liquids such as [BMIm]PF<sub>6</sub>, which can function as a recyclable reaction media and catalyst support. The results were again compared to the analogous batch reactions and demonstrated higher yields when performed in flow (Scheme 1).<sup>24</sup> Furthermore, the palladium-catalyzed carbonylative Sonogashira coupling yielded only the acetylenic ketone when performed in microflow but also formed the Sonogashira coupled byproduct when run under batch conditions. When diethylamine was used as the nucleophilic partner, the microflow procedure gave a mixture of the amide (**14**) and  $\alpha$ -ketoamide (**15**), with the latter being the main product (95:6–87:13, **15/14**). This was in drastic contrast to what was observed by the Long group, who instead obtained the amide as the main product.<sup>23</sup> This was probably due to the higher pressures used in the Ryu plug flow system (15–20 atm), which allows for a greater concentration of dissolved carbon monoxide in the solvent, giving a higher proportion of the double-addition  $\alpha$ -ketoamide product.

The specific conditions leading to the formation of the  $\alpha$ -ketoamides was studied by the Buchwald group in an attempt to avoid its generation.<sup>25</sup> As would be expected, it was concluded that in a microflow reactor either elevating the temperature or decreasing the pressure increases the selectivity for the formation of the amide with carbon monoxide added as an annular flow.

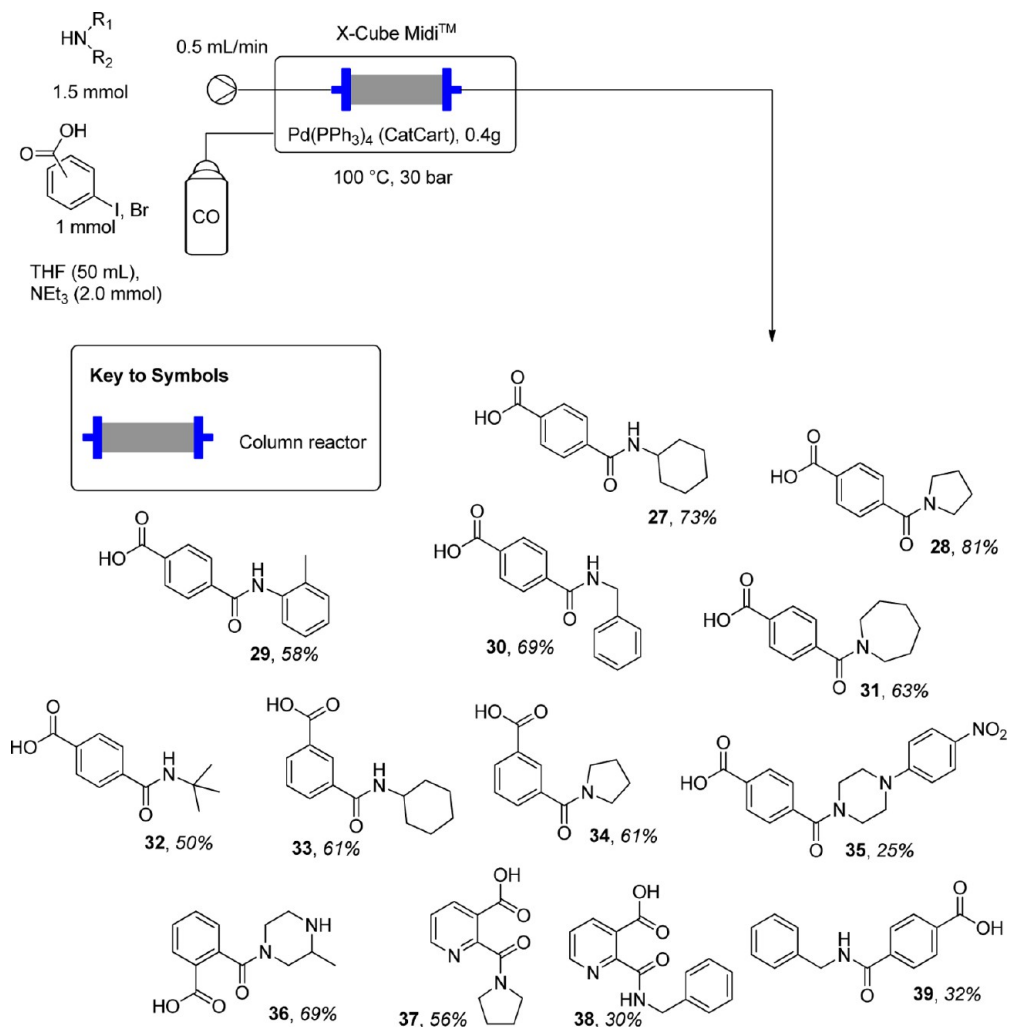
The Long group additionally reported on the use of flow carbonylation for the synthesis of amides comprising radio-labeled <sup>11</sup>CO.<sup>26</sup> In this reaction, a triphasic reaction system utilizing a silica-supported palladium diphosphine catalyst was employed as a packed bed reactor, produced by loading the catalysts into a length of Teflon tubing. Very good yields were achieved for electron-deficient bromo-arenes (99% yield, 3 examples), but much lower yields were obtained for the more challenging electron-rich systems (23–26%, 2 examples). This would correlate well with the need for longer reaction times for electron-rich systems that would be difficult to achieve in the low residence time reactor assembled for this study.

Miller et al. showed that the use of a chip-based microfluidic system with an annular CO flow profile could be used to rapidly screen for ligand activity in amino-carbonylations. A simple coupling between iodobenzene **1a** and benzylamine **2** was used as a standard test reaction.<sup>27</sup> A total of eight different catalysts were screened across a range of temperatures varying from 75 to 150 °C using very short residence times (2 min). Generally, catalysts performed better as the temperature was increased, with PdCl<sub>2</sub>(dppf), PdCl<sub>2</sub>(dppp), PdCl<sub>2</sub>(Biphenphos), PdCl<sub>2</sub>(DPEphos), PdCl<sub>2</sub>(Synphos), and Pd(PPh<sub>3</sub>)<sub>4</sub> giving good GC yields (>75%) at 150 °C, whereas PdCl<sub>2</sub>(BINAP) still gave only 45% GC yield even at the highest temperature of 150 °C. The best precatalyst was found to be PdCl<sub>2</sub>(Xanthphos), which gave 94% GC yield at the higher temperature range and was found to give even an 85% GC yield at 75 °C.

Scheme 2. Comparison between Annular and Segmented Flow in Amino-Carbonylation System



Scheme 3. Amino-Carbonylation of Halogenated Aryl Carboxylic Acids in Flow Using the X-Cube

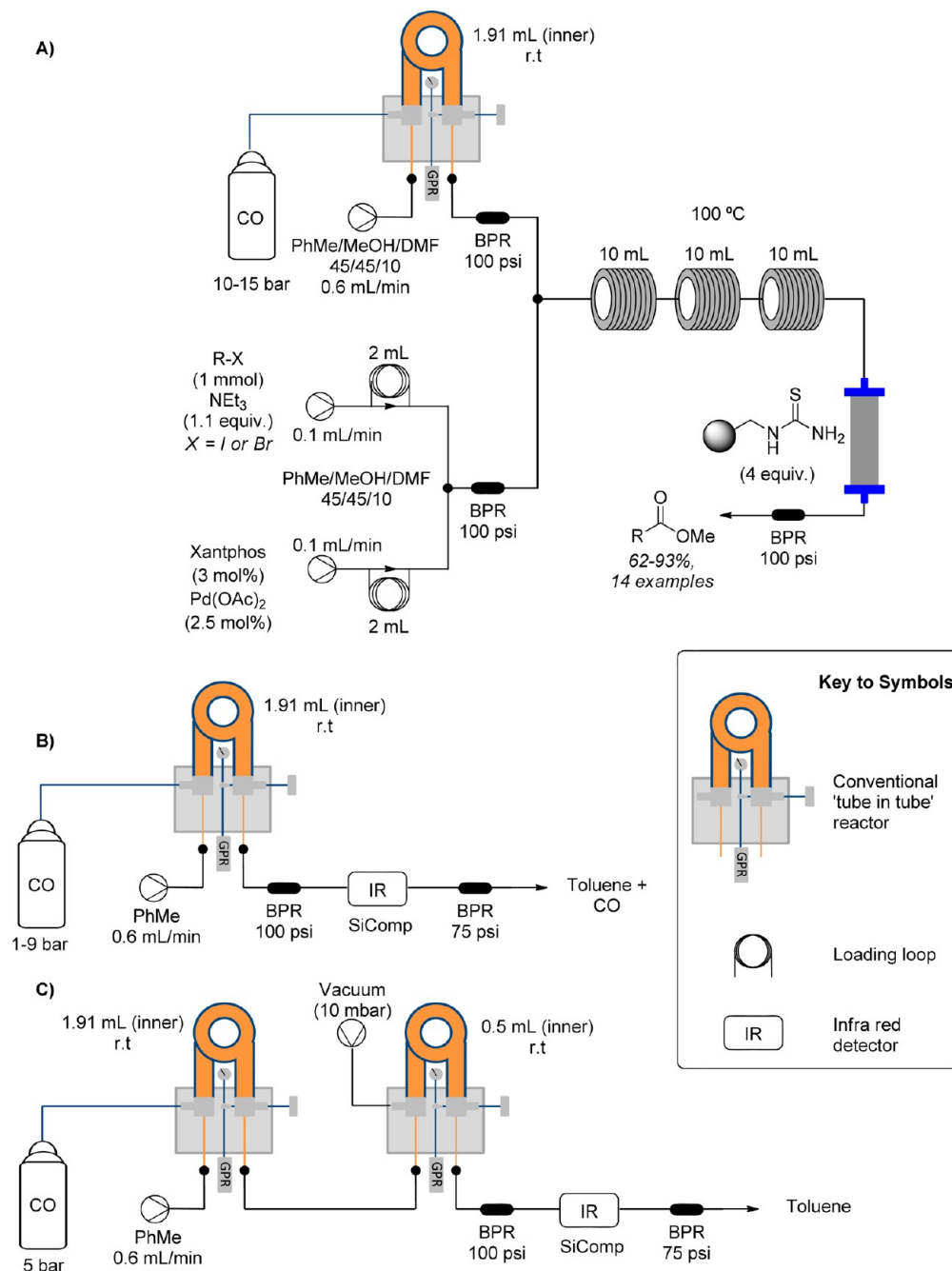


The Ryu group described their continuing studies of carbonylation chemistry by expanding into radical carbonylation of aliphatic halides.<sup>28</sup> They employed a microfluidic flow system with the carbon monoxide delivered through a simple T-piece connector (Table 4). It was shown using the radical initiator V-65 [(2,2'-azobis(2,4-dimethylvaleronitrile); half-life time, 12 min at 80 °C] in the presence of 1-bromododecane (16), tributyltin hydride, and carbon monoxide at 80 °C that

full conversion of the 1-bromododecane was achieved in 12 min, with a 77% isolated yield of tridecanal (17). The same continuous microflow system was also used with silicon-based hydride donors delivering various aldehydes, unsymmetrical ketones, and a  $\delta$ -lactam all in good to excellent yields.

The de Mello group and collaborators reported a comparison between the use of annular flow and plug flow for amino-carbonylation reactions (Scheme 2).<sup>29</sup> Even though the annular

Scheme 4. (A) Methoxy Carbonylation in Flow Using the Tube-in-Tube Reactor Design, (B) Use of In-Line IR Monitoring To Determine Concentration of Dissolved Carbon Monoxide in Solvent, and (C) Use of a Second Tube-in-Tube under Vacuum To Remove the Dissolved Carbon Monoxide



flow method was shown to be efficient, it was limited to short residence times (2–5 min). The plug flow method could enable longer residence times and had a reduced tendency to block the reactor due to formation of Pd black particulates during carbonylation. It was reported that the use of the Pd dimer [Pd<sub>2</sub>(μ-I)<sub>2</sub>(P<sup>t</sup>Bu<sub>3</sub>)<sub>2</sub>] served as an excellent precatalyst for aminocarbonylation, being far superior to many other previously reported catalysts.

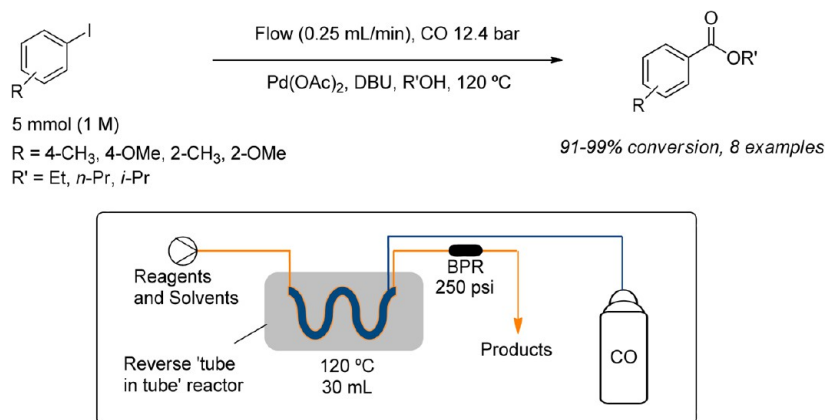
The amino-carbonylation of halogenated aryl carboxylic acids with various amines has also been reported by Csajági et al. using a commercial pressurized continuous flow reactor (Scheme 3).<sup>30</sup> The substrates were passed through a phosphine-immobilized version of Pd(PPh<sub>3</sub>)<sub>4</sub> to generate

moderate to good yields of a variety of amide products (27–39) that were prepared in very short residence times (~2 min).

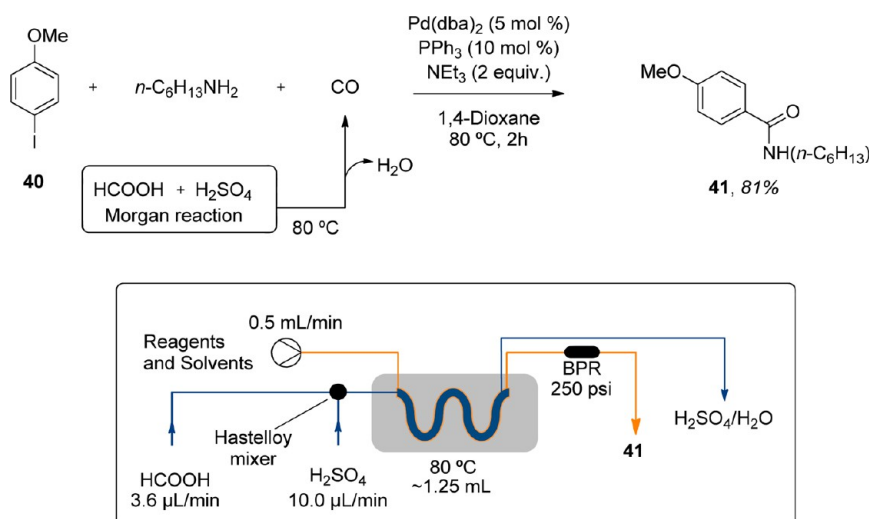
The use of a conventional tube-in-tube configuration for carbonylation reactions was reported by the Ley group (Scheme 4).<sup>31</sup> In that publication, a selection of aryl iodides, bromides, and vinyl iodides was tested, with most of the substrates giving good to excellent yields (62–93% yields, 14 examples). A solvent mixture of toluene, methanol, and dimethylformamide was used. Methanol was utilized as the nucleophilic partner, and dimethylformamide was found to be beneficial for stabilizing the palladium catalyst and thus preventing the formation of palladium black. An in-line scavenger cartridge packed with polymer-bound thiourea



Scheme 5. Alkoxy carbonylation of Aryl Iodides in Flow Using the Reverse Tube-in-Tube Reactor



Scheme 6. Aminocarbonylation of 40 in Flow Using the Morgan Reaction in the Reverse Tube-in-Tube Reactor



resin was used to remove the palladium from the reaction mixture, making the purification of the crude material easier. Furthermore, a ReactIR detector was deployed in-line to monitor the carbon monoxide concentration in the flow stream. This was used to find the optimum pressure to give the highest carbon monoxide concentration in the liquid stream. The use of a second tube-in-tube system under vacuum to remove the excess dissolved carbon monoxide as an in-line process was also described. The removal of residual carbon monoxide was also monitored using ReactIR. This is especially relevant for industrial processes that make use of carbonylation reactions to facilitate detection and possibly recycle the excess gas.

The use of a reverse tube-in-tube configuration was exemplified by Leadbeater and co-workers for the carbonylation of several aryl iodides to give the alkoxy carbonylative products in excellent conversions (91–99%, 8 examples) (Scheme 5).<sup>32</sup> The same group also published a carbonylative system in which a plug flow system was used, and, although it showed superior yields to the batch systems, it was still not as efficient as the reverse tube-in-tube system.<sup>33</sup>

The Ryu group devised an innovative use of the tube-in-tube system (Scheme 6).<sup>34</sup> Instead of directly dosing carbon monoxide to the inner gas-permeable tube, concentrated sulfuric acid and formic acid were mixed to form carbon monoxide *in situ* (Morgan reaction), which was then shown to be available for Heck aminocarbonylation. Two flow streams

were directed in a cocurrent flow configuration for the work described; however, no specific mention was made to acknowledge if the counterflow system was also tested.

The same group published a similar protocol for the carbonylation of alcohols through the Koch–Haaf reaction.<sup>35</sup> Again, concentrated sulfuric acid and formic acid were directly mixed with the substrate in a Hastelloy-made micromixer. The acid mixture forms carbon monoxide *in situ* through the Morgan reaction, which, in turn, reacts with the carbocation formed after the elimination of the hydroxyl group. The authors showed that there were selectivity limitations and that the reaction in flow gave little improvement compared to batch protocols (Table 5). Additionally, they also showed a multigram scale-up version for the synthesis of 1-adamantane-carboxylic acid 43 (Scheme 7).

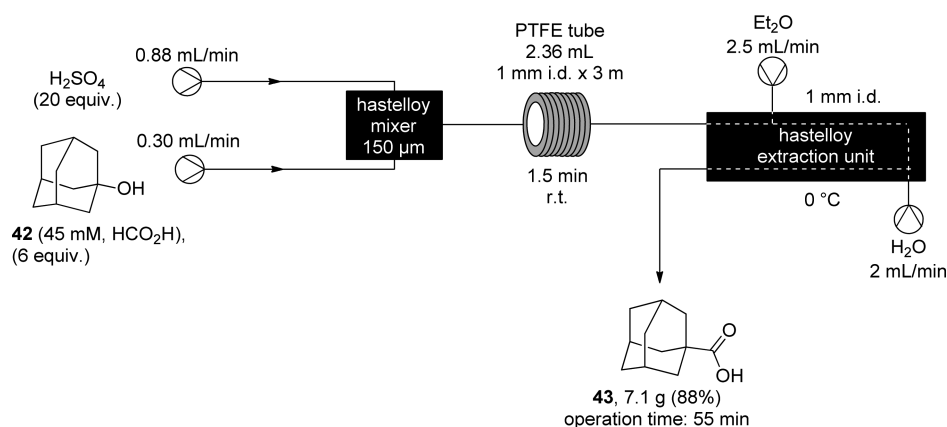
Recently, a conventional tube-in-tube system was used to expand the scope of carbonylation reactions in flow such as aminocarbonylations (79–93%, 5 examples), alkoxy carbonylations (60–95%, 9 examples), and hydroxycarbonylations (58–100%, 5 examples), including some intramolecular examples to form lactams and a lactone (95%, 3 examples).<sup>36</sup> An interesting addition was the use of a gaseous amine (dimethyl amine) in the hydrazine-promoted amino-carbonylation process, achieved by coupling two conventional tube-in-tube systems in series (Scheme 8). In the initial screening, a higher concentration of substrates was investigated, but this gave low conversions,

Table 5. Comparison of Koch–Haaf Reactions of Adamantanols in Microflow and Batch<sup>a</sup>

Entry	Substrate	Reactor	Conditions	Product (yield) <sup>b</sup>
1		microflow	T: 20 °C Flow rate (42/HCO <sub>2</sub> H): 0.30 mL/min Flow rate (H <sub>2</sub> SO <sub>4</sub> ): 0.88 mL/min Residence time: 2 min <sup>c</sup> Residence time: 1.5 min <sup>d</sup>	 43, 89%
2		batch	T: 15–20 °C Addition time: 5 min Reaction time: 2 min	 43, 92%
3		microflow	T: 20 °C Flow rate (44/HCO <sub>2</sub> H): 0.30 mL/min Flow rate (H <sub>2</sub> SO <sub>4</sub> ): 0.88 mL/min Residence time: 2 min <sup>c</sup> Residence time: 1 min <sup>d</sup>	  82% (58:42)
4		batch	T: 17–20 °C Addition time: 5 min Reaction time: 1 min	  65% (14:86)
5		microflow	T: 20 °C Flow rate (46/HCO <sub>2</sub> H): 0.01 mL/min Flow rate (H <sub>2</sub> SO <sub>4</sub> ): 0.3 mL/min Residence time: 20 min <sup>c</sup> Residence time: 2.5 min <sup>d</sup>	   97% (23:53:24) 49 (47:53)
6		batch	T: 17–20 °C Addition time: 3 min Reaction time: 10 min	   83% (19:62:19) 49 (47:53)

<sup>a</sup>Substrate (4 mmol), HCO<sub>2</sub>H (6 equiv), H<sub>2</sub>SO<sub>4</sub> (20 equiv). <sup>b</sup>Isolated yield after column chromatography on SiO<sub>2</sub>. <sup>c</sup>Calculated. <sup>d</sup>Observed.

## Scheme 7. Multigram Scale Flow Synthesis of 1-Adamantanecarboxylic Acid (43)

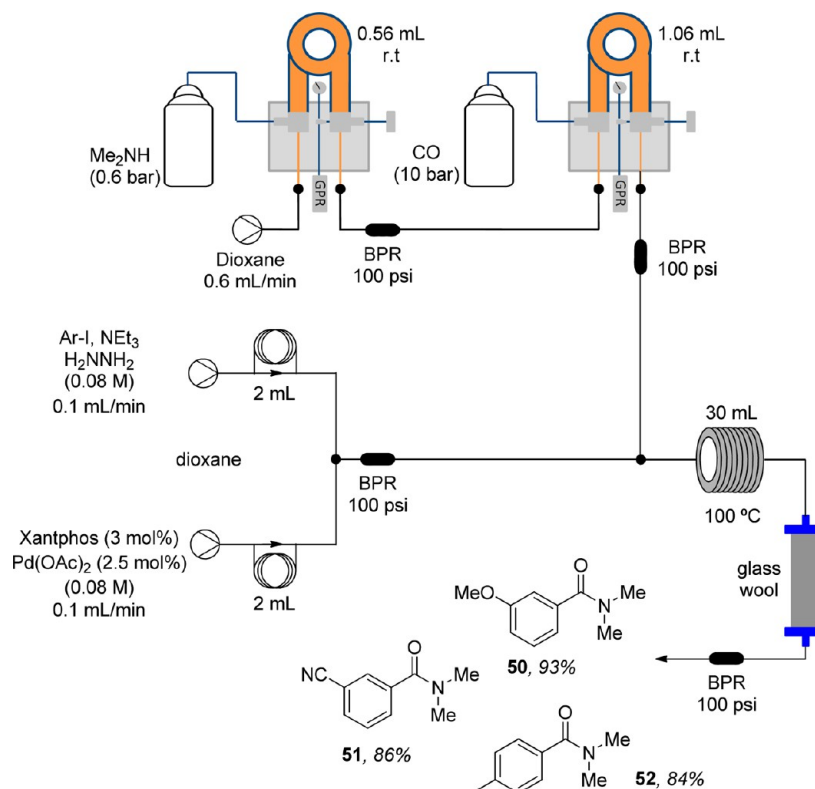


indicating that the reaction was limiting in at least one of the gases used. An alternative setup, where the substrates were directly passed through the tube-in-tube reactors to saturate the streams, was also tested, but this showed low conversions. Eventually, the system setup shown in Scheme 8 was used. This required the use of several back-pressure regulators positioned at different locations within the setup to stabilize the flow and to maintain the required system pressure. Additionally, a small column packed with glass wool was employed after the reactor to filter off any precipitate formed during the reaction, mainly

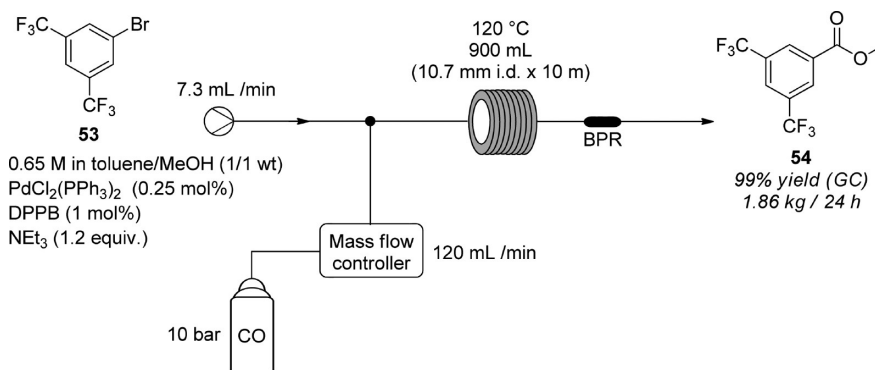
palladium black, which could lead to the final back-pressure regulator being blocked.

A near stoichiometric (1.2 equiv) amount of carbon monoxide was shown to be effective for the continuous flow Heck-carbonylation of 1-bromo-3,5-bis(tri-*n*-butylmethyl)-benzene (53). The reaction was promoted by PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst with 1,4-bis(diphenylphosphino)butane (dppb) as the supporting ligand.<sup>37</sup> A kilogram-scale production of product 54 was successful when using a large tubular reactor ~900 mL (10.7 mm i.d. × 10 m) at 0.65 M concentration to

Scheme 8. Aminocarbonylation in Flow Using Two Gases via Conventional Tube-in-Tube Reactors



Scheme 9. Heck Carbonylation of Bromide 45 in Continuous Flow



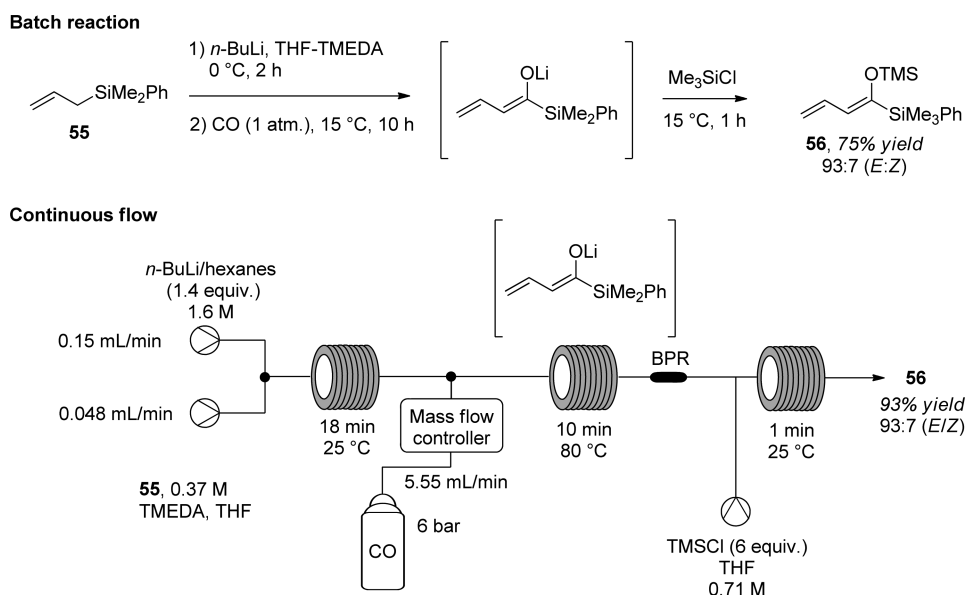
produce a throughput of 1.86 kg/day while still maintaining the 99% yield originally obtained for the smaller scale reaction (Scheme 9). In addition, the flow deprotonation of allylsilane (55) to form a 1-silylallyllithium intermediate that was then carbonylated and quickly quenched with trimethylsilane chloride to furnish a dienol silyl ether 56 in excellent yield and *E/Z* ratio (93%, 97:3) was reported.<sup>38</sup> A comparison with the batch protocol indicated that the flow process was more efficient and very straightforward to run (Scheme 10). The flow protocol was subsequently expanded to a wider selection of alkylsilanes and electrophiles, all of which gave good to excellent yields and selectivities (77–88% yields, 91:9–97:3 (*E/Z*), 5 examples).

A synthesis of a phenyl isocyanate starting from nitrobenzene (57) in flow was reported by Takebayashi and co-workers using carbon monoxide as a reductant (Scheme 11).<sup>39</sup> The carbon monoxide was delivered at a 90° angle to the liquid flow through a T-piece connector, resulting in a segmented flow

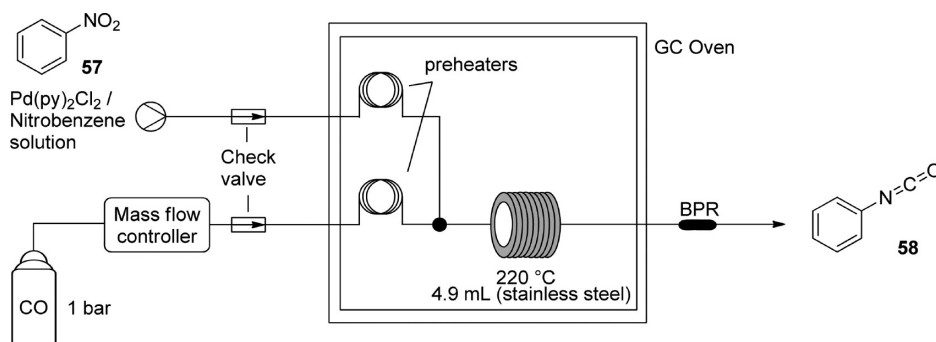
system, which was directed into a tubular reactor heated at 220 °C. The direct comparison of the corresponding batch protocol demonstrated that the flow procedure gave a higher yield, although the authors did not quantify the yield or how it was measured. It was shown that changing the inner diameter (i.d.) of the tubular reactor had a significant impact on the reaction efficiency. The use of a 1.0 mm i.d. tube reactor gave a lower yield than using a 0.5 mm i.d. tube reactor. This was explained as being due to a higher surface to volume ratio of the carbon monoxide with the liquid plug; thus, a smaller inner diameter tube will give a higher concentration of dissolved carbon monoxide in the reaction mixture.

**Hydrogen.** Hydrogen is another important synthesis gas. Hydrogenation reactions are frequently used in both research and at production scale, especially in the petrochemical industry to reduce alkenes and aromatic rings and in the food industry to reduce polyunsaturated fatty acids from vegetable oils to produce solid or semisolid fats such as those found in

**Scheme 10. Formation, Carbonylation, and Quenching of the 1-Silylallyllithium Intermediate To Give the Dienol Silyl Ether in Flow as Well as Comparison with the Batch Protocol**



**Scheme 11. Flow Carbonylation of Nitrobenzene to Give Phenylisocyanate 58**



margarine. Hydrogen also carries a risk due to its high flammability and potential for extremely exothermic detonation. In addition, most hydrogenation reactions tend to be performed under high pressures; therefore, the risk of using hydrogen is substantially increased. Hydrogenation reactions using heterogeneous and homogeneous catalysts in continuous flow are well-documented and have been extensively reviewed;<sup>40</sup> hence, this review will focus on a select set of publications that demonstrate some alternative approaches.

ThalesNano has developed several flow reactors, of which the H-Cube series has been specifically tailored for the generation and direct use of heterogeneous hydrogenation reactions in flow.<sup>41</sup> The commercial units are now routinely used in various hydrogenation reactions. The system also can be automated to run in a high-throughput manner, allowing multiple samples to be sequentially processed or various conditions to be screened.<sup>42</sup> Alternatively, larger quantities can be produced through the use of longer production runs as well as using sequentially scaled reactors (H-Cube mini → H-Cube → H-Cube midi).<sup>43</sup>

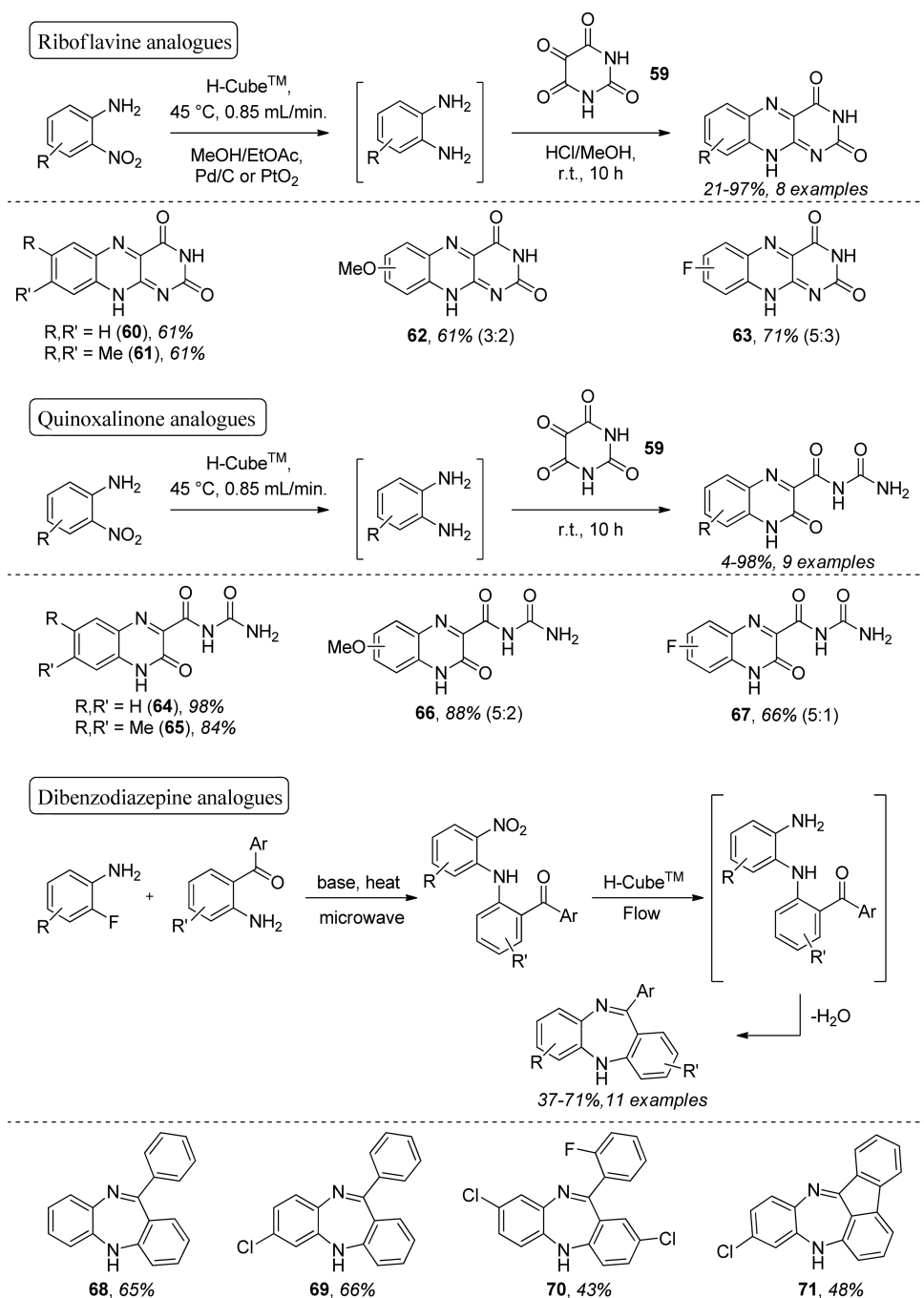
Recently, our group demonstrated the flow hydrogenation of various 2-nitroanilines using the H-Cube to form reactive 1,2-diaminobenzene intermediates as part of the synthesis of riboflavin analogues (21–98% yield, 8 examples), quinoxalinone analogues (4–98% yields, 9 examples), and dibenzo-

diazepine derivatives (37–72% yields, 11 examples) (Scheme 12).<sup>44</sup> The regioselectivity of some of the products was not always optimal, with a mixture of the two regioisomers being observed. However, importantly, the short residence time (4–6 min) required for the hydrogenation step gave substantially less decomposition of the unstable diamine intermediates, meaning that this flow approach was beneficial.

A large scale hydrogenation has been conducted using the Corning advanced-flow reactor.<sup>45</sup> This multiple stacked chip reactor consists of a number of coupled units (15 glass chips, total internal volume of 125 mL) with “heart cells” to improve the flow of pumped slurries (Figure 5). The hydrogenation process was tested for the effect of temperature, residence time, hydrogen molar ratio, catalyst loading, and concentration of reagents on conversion. The batch process gave excellent chemoselectivity (99%) but low conversion (<20%). Under the final optimized flow conditions, an efficiency of 0.43 kg of product per hour could be processed, which can be extrapolated to yield up to 200 tonnes per year with 98% conversion and 95% selectivity. Unfortunately, no details about the specific chemical transformation were given and thus the conversions, selectivity, and productivity cannot be compared.

A continuous flow homogeneous hydrogenation of alkenes using a conventional tube-in-tube reactor setup was published in 2011 (Scheme 13)<sup>46</sup> using hydrogen gas and [Ir(COD)

Scheme 12. Synthesis of Riboflavine, Quinoxalinone, and Dibenzodiazepine Analogues through a Heterogeneous Hydrogenation Step



(PCy<sub>3</sub>)<sup>+</sup>PF<sub>6</sub><sup>−</sup> as the catalyst (Table 6). As a foresight to increasing the safety of the system when scaling up, several experiments were conducted to find a balance between a short residence time and sufficient hydrogen pressure to minimize the hydrogen excess and thus outgassing after the back-pressure regulator. A total residence time of 93 s and a hydrogen pressure of 25 bar were deemed to be the optimized conditions. A degassing system was also disclosed, which utilized a camera to evaluate bubble sizes for quantification of the amount of hydrogen gas remaining in the system. A standard digital photograph was taken and used to create a snapshot of the flow stream. This image was automatically pixelated and contrast controlled to enable counting of the void area (white in Figure

6) and solution filled area (red in Figure 6). A calculation could then be performed to determine the proportion of gas bubbles, and based upon the system pressure, a good indication of the gas concentration could be derived.

The Leadbeater group used RhCl(PPh<sub>3</sub>)<sub>3</sub> (Wilkinson's catalyst) with a reverse tube-in-tube reactor to perform a series of homogeneous flow hydrogenation reactions (Scheme 14).<sup>47</sup> Using optimized conditions, substrates were screened to determine which functionalities were tolerated. Most of the alkenes gave good to excellent yields (77–99% yield, 11 examples), but certain functionalities were not tolerated, such as an alcohol, which chelates with the metal complex, a diacetate functionality, which undergoes a Tsuji–Trost type



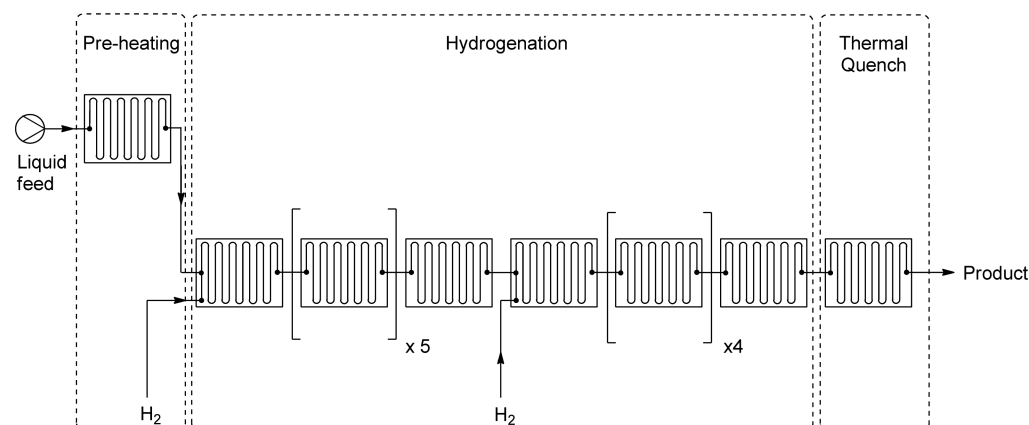


Figure 5. Glass fluidic modules used for the slurry hydrogenation.

### Scheme 13. Homogenous Hydrogenation in Flow Using the Tube-in-Tube Reactor

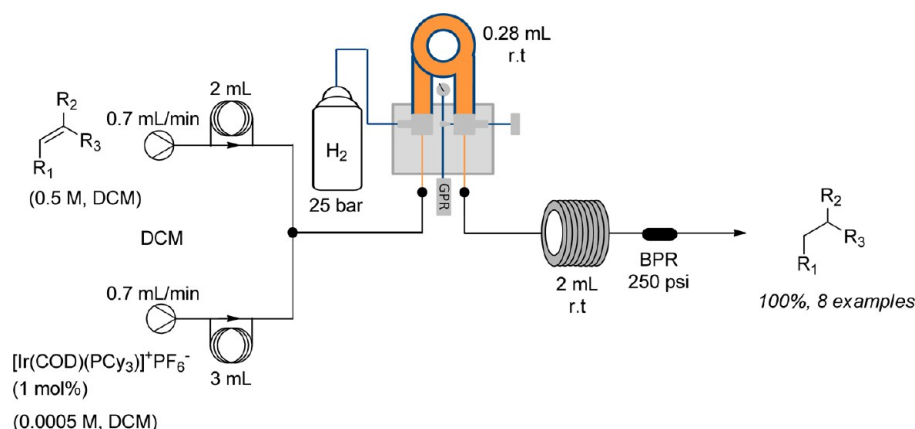


Table 6. Homogenous Flow Hydrogenation

Entry	Substrate	Product	Conversion <sup>a</sup>	Yield <sup>b</sup>
1			100%	Quant.
2			100%	Quant.
3			100%	Quant.
4			100%	Quant.
5			100%	Quant.
6			100%	Quant.
7			100%	Quant.
8			100%	Quant.

<sup>a</sup>Conversion to product based on <sup>1</sup>H NMR spectroscopy. <sup>b</sup>Isolated yield after removal of solvent.

reaction (elimination of one acetate moiety) followed by polymerization, and also an aldehyde moiety, which underwent decarbonylation at the high temperatures used.<sup>48</sup>

The reactor setup for the transformations was very straightforward but required a diluent stream to prevent issues caused by precipitate blocking the back-pressure regulator

positioned at the exit of the reactor. Consequently, an additional stream of acetone was directed to mix with the reactor output stream via a T-piece, just after the second reactor and just before the back-pressure regulator; this ensured that any precipitate formed from the dimerization of the catalysts or the formation of insoluble  $\text{HRhCl}_2(\text{PPh}_3)_2$  was solubilized. To evaluate the scalability of the reaction, 90.0 mmol of *trans*-chalcone in 30 mL of DCM (3 M) was hydrogenated. This gave an excellent yield (99% yield) and corresponds to a throughput of 45 mmol/h under continuous operation.

The Ley group has demonstrated the asymmetric hydrogenation of trisubstituted olefins, having tested several homogeneous catalysts. UbaPhox (**91**) exhibited the highest reactivity and selectivity.<sup>49</sup> It was found that a setup consisting of two tube-in-tube reactors separated by a mixing chip was optimal (Scheme 15). The second tube-in-tube reactor replenishes the hydrogen needed to increase the diastereoselectivity of **92**, with the mixing chip in between serving to ensure turbulent mixing of substrate and catalyst, which was shown to improve conversion.

**Syngas: Carbon Monoxide and Hydrogen in a 1:1 Mixture.** The mixture of carbon monoxide and hydrogen, normally in a 1:1 volumetric ratio, commonly known as syngas (synthesis gas), has been used in flow reactions by the Ley group.<sup>50</sup> Initially, it was reported on simple styrene substrates to furnish mixtures of branched and linear aldehydes. Optimization focused on the rhodium catalyst, with  $[\text{Rh}(\text{CO})_2(\text{acac})]$  and triphenylphosphine giving the best con-

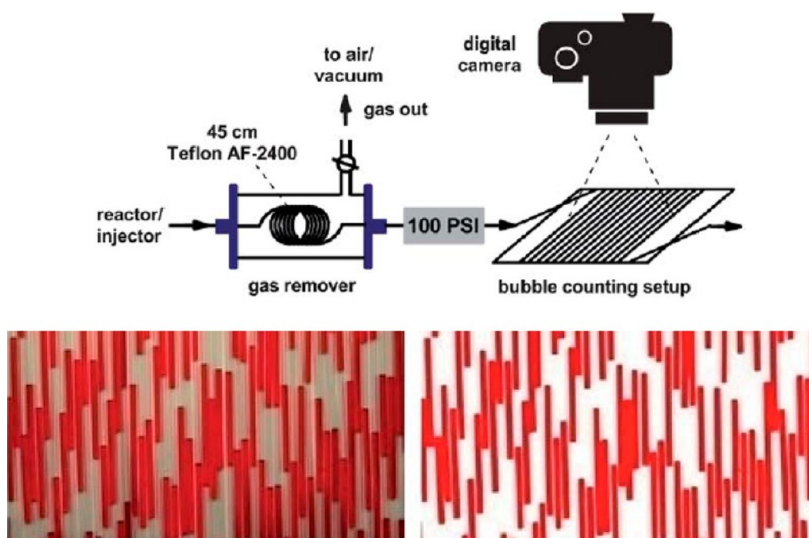
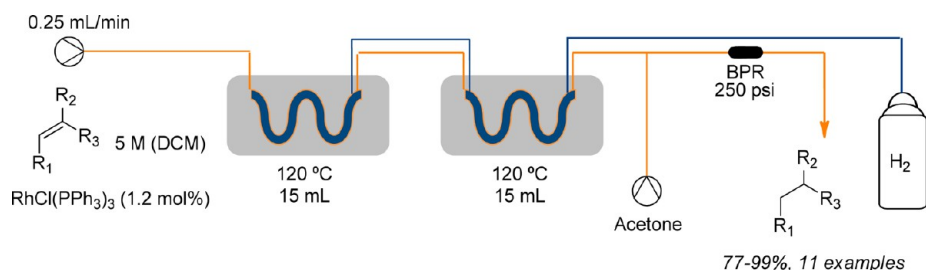
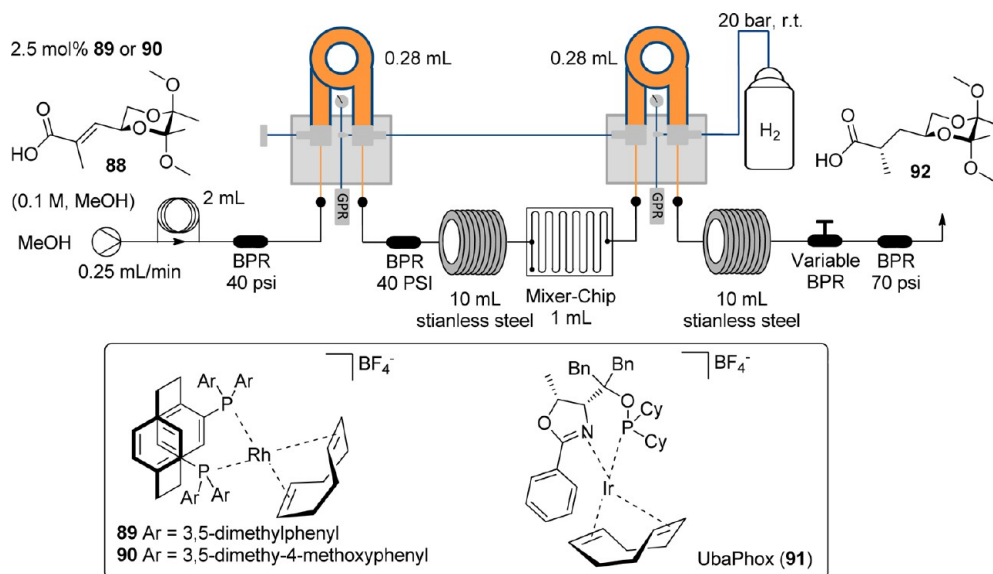


Figure 6. Sudan red dye in DCM; lower image 1 (left) is the photo, and lower image 2 (right) is the pixelated rendering.

#### Scheme 14. Homogenous Hydrogenation of Alkenes Using Reverse Configured Tube-in-Tube Reactors



#### Scheme 15. Homogenous Asymmetric Hydrogenation of Substrate 88 in Continuous Flow

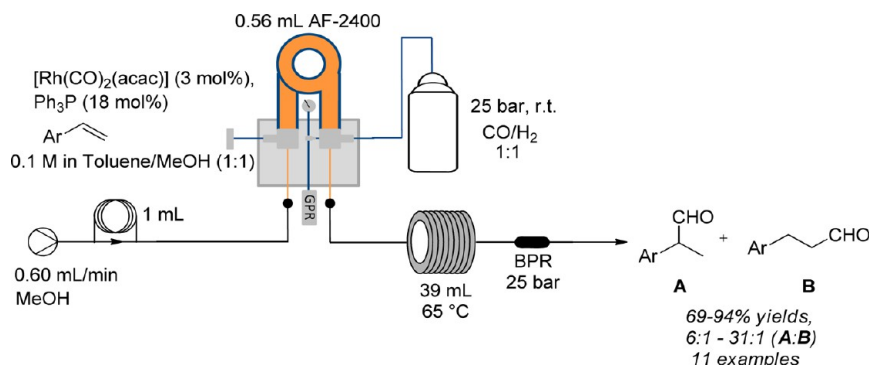


version and selectivity. A solvent screen revealed that a 1:1 mixture of methanol/toluene was the most effective. In addition, temperature, flow rate, amount of ligand, and pressure of the syngas used were systematically assessed. The reaction generally gave good yields (69–94%, 11 examples) and regioselectivities for the branched isomer (6:1–31:1). Styrenes with electron-withdrawing substituents showed improved yields and regioselectivities compared to those possessing electron-

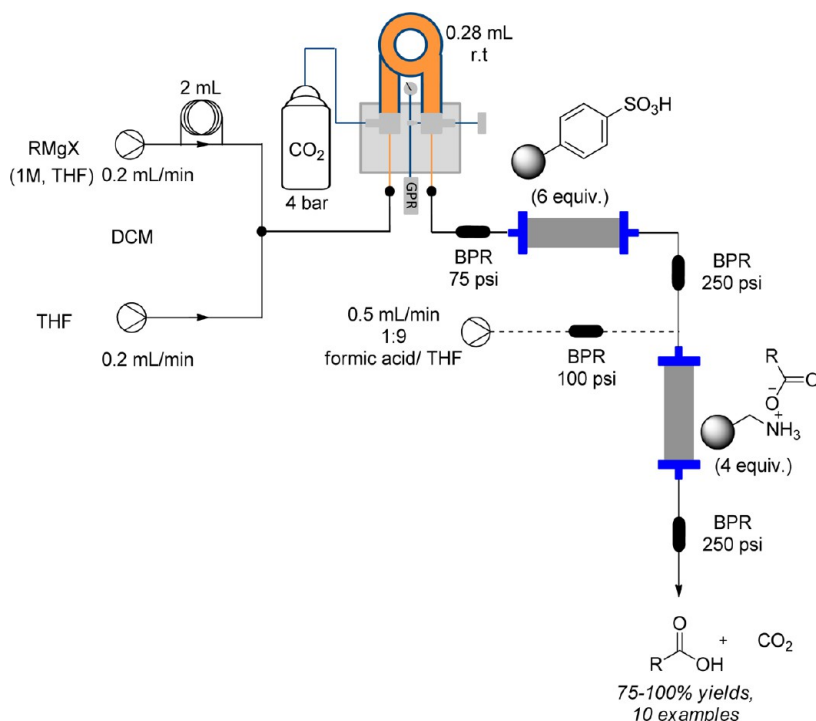
donating groups, which was consistent with previous batch results (Scheme 16).

**Carbon Dioxide.** Carbon dioxide is normally used as a building block in synthesis by making use of its weak electrophilic characteristic. A flow procedure to trap carbon dioxide in the formation of carboxylate group has been developed. Grignard substrates were passed through a conventional tube-in-tube reactor to deliver the carbon dioxide

Scheme 16. Selective Flow Hydroformylation of Styrenes



Scheme 17. Flow Carboxylation of Grignard Substrates Using Carbon Dioxide



(Scheme 17).<sup>51</sup> Optimum conditions were determined at 4 bar of carbon dioxide, enabling near quantitative conversions even at moderate flow rates (0.4 mL/min, residence time = 42 s). A set of 10 different carboxylic acids was prepared in good to excellent yields (75–100% yields); unfortunately, no examples using electron-withdrawing substituents were reported. An efficient catch-and-release protocol was used to facilitate in-line purification of the carboxylic acid using a cartridge containing a polymer-supported ammonium hydroxide species (A-900). Following trapping of the carboxylic acid, the cartridge was washed with THF to remove any unwanted organic impurities and then “released” by treatment with a solution of formic acid in THF (1:9) to yield the pure carboxylic acid. Similarly, the Rutjes group reported on the formation of benzoic acid through the hydroxycarbonylation of phenylmagnesium bromide in flow, delivering a throughput of 0.52 g/h using a commercial (FlowStart *Evo*, Future Chemistry) pumping system.<sup>52</sup>

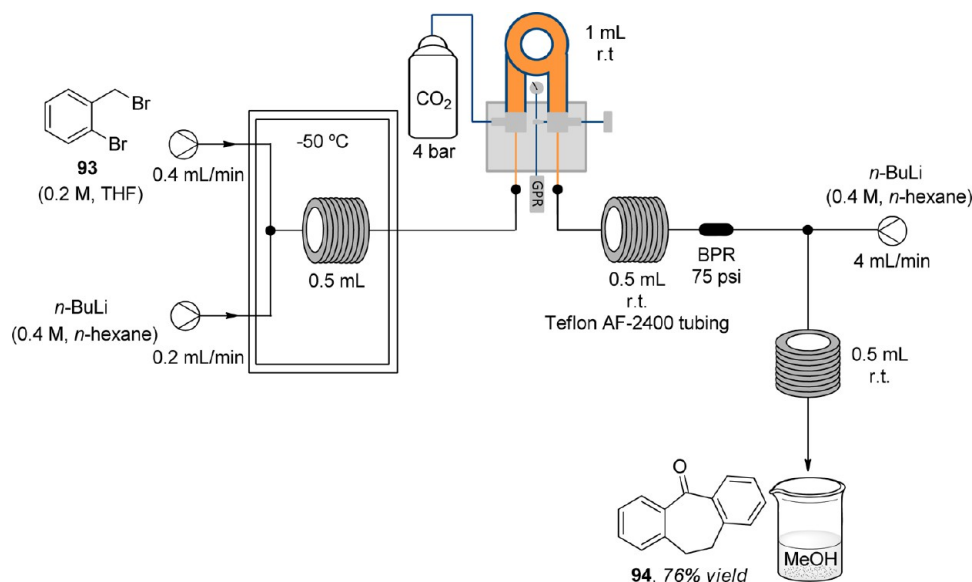
The flow synthesis of amitriptyline (**94**) using carbon dioxide in flow was reported by the Kirschning group.<sup>53</sup> As part of the process development, it was noted that excess carbon dioxide was possibly reacting with the *n*-BuLi required for the second

stage Parham cyclization (Scheme 18). Ultimately, the excess carbon dioxide was removed by passing the liquid stream through a Teflon AF-2400 tube acting to degas the pressurized flow stream prior to adding the *n*-BuLi and yielding the product in an isolated yield of 76%.

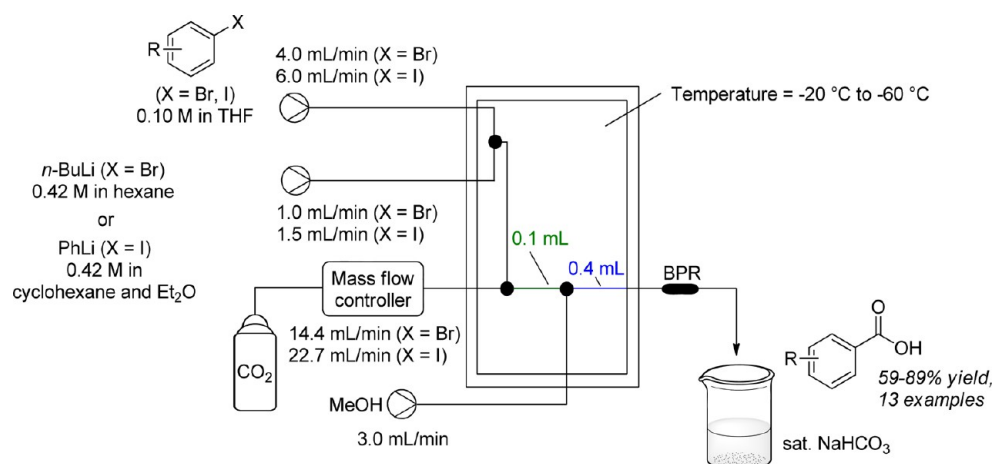
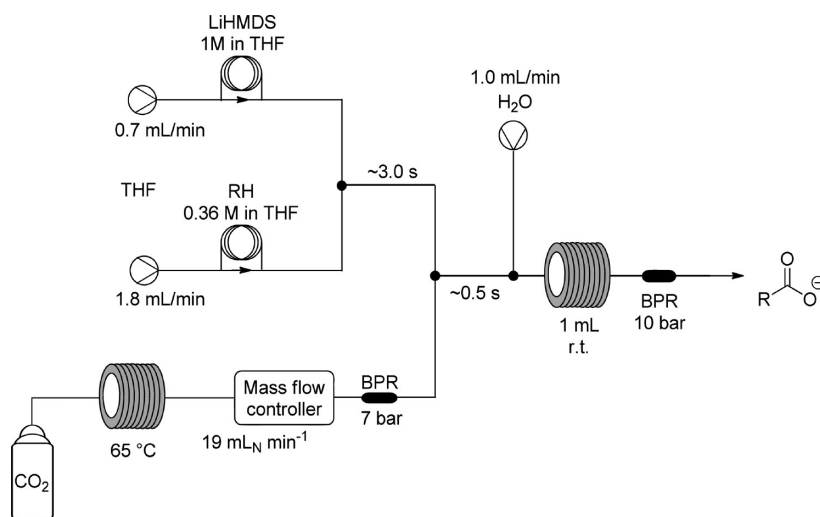
A related transformation was performed by the Yoshida group, using *in situ* generated organolithium species (Scheme 19).<sup>54</sup> The organolithium intermediate formed by lithium halogen exchange was immediately trapped with carbon dioxide in an annular flow setup. A stream of methanol quenched the excess *n*-BuLi prior to collection of the product into a saturated sodium bicarbonate solution. Beneficially, the flow protocol did not yield any benzophenone or triphenyl methanol derivatives, which are normally observed in the corresponding batch reactions. Using this setup (Scheme 19), a selection of carboxylic acids was synthesized in good yields (59–89% yield, 13 examples), representing a range of different electronics that do not appear to influence the yield of the carboxylic acid.

A similar concept was later demonstrated by the Kappe group, where they used lithium *bis*(trimethylsilyl)amide (LiHMDS) or lithium diisopropylamide (LDA) solutions to

Scheme 18. Synthesis of Amitriptyline Using Carbon Dioxide in Flow

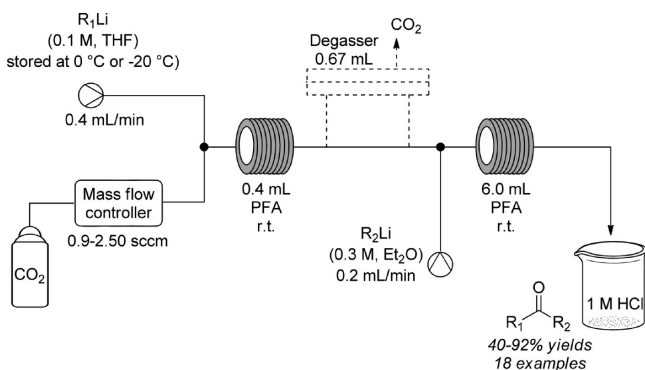
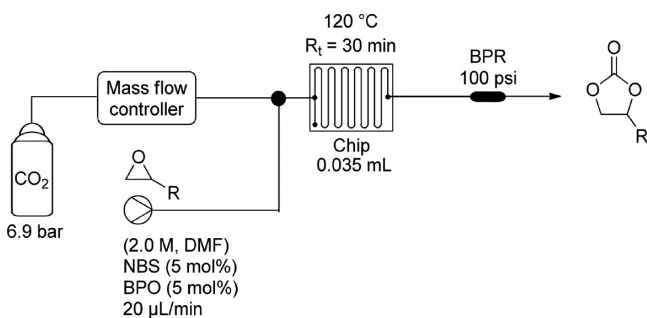


Scheme 19. Flow Carbonylation of Organolithiums Using Carbon Dioxide

Scheme 20. Flow Setup for the Carboxylation of Lithiated Species Using CO<sub>2</sub> Gas

achieve the lithiation of terminal alkynes or heterocycles.<sup>55</sup> The lithiation was shown to happen very rapidly ( $\sim 0.5$  s at room

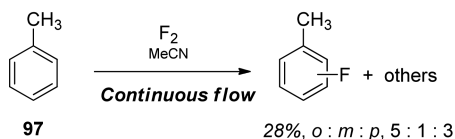
temperature), but they opted for a  $\sim 3$  s residence time, after which the lithiated substrate was carboxylated with carbon

Scheme 21. Flow Setup for the Synthesis of Unsymmetric Ketones Using CO<sub>2</sub> GasScheme 22. Microflow Synthesis of Cyclic Carbonates through Bromine-Catalyzed Conversion of CO<sub>2</sub> and Epoxides

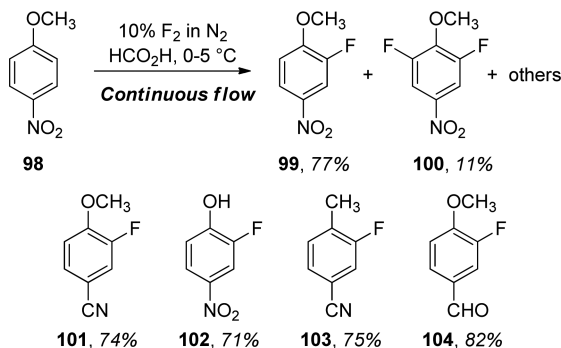
dioxide through a T-mixer. In order to stabilize the CO<sub>2</sub> flow, the gas was preheated at 65 °C before going through the mass flow controller (Scheme 20). Additionally, a water quench was introduced before the back-pressure regulator to dissolve any small amounts of precipitate formed during the reaction. Using the optimized conditions, a number of alkynes were carboxylated, generally giving very good yields (66–90% yields, 8 examples). A couple of examples gave no results due to problems encountered with the reactor clogging. The carboxylation of some additional heterocycle substrates was

Scheme 24. Continuous Flow Fluorination of Several Aromatic Systems

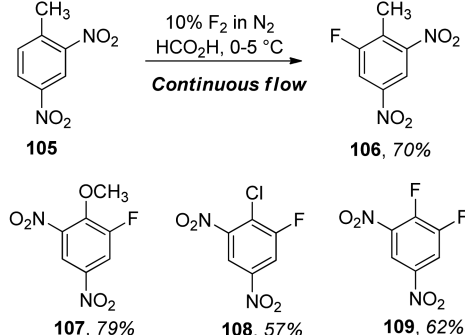
Direct fluorination of toluene using a falling film microreactor (FFMR)



Fluorination of 1,4-disubstituted aromatic derivatives

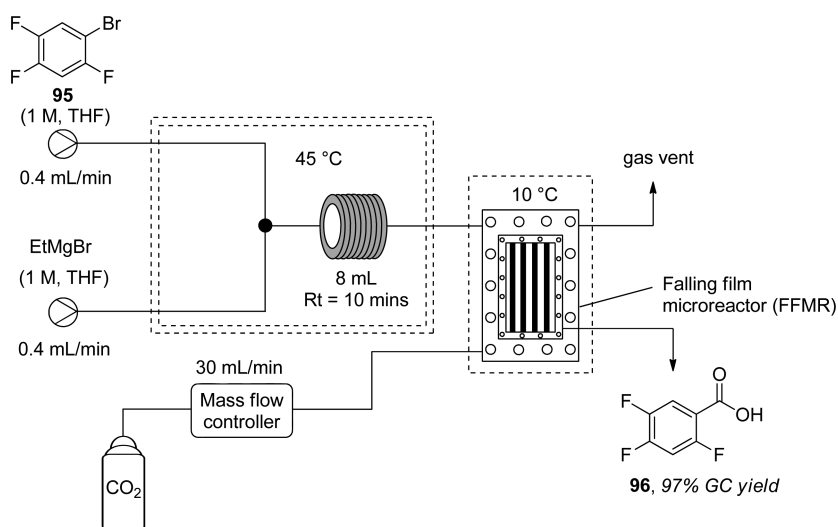


Fluorination of 1,3-disubstituted aromatic derivatives



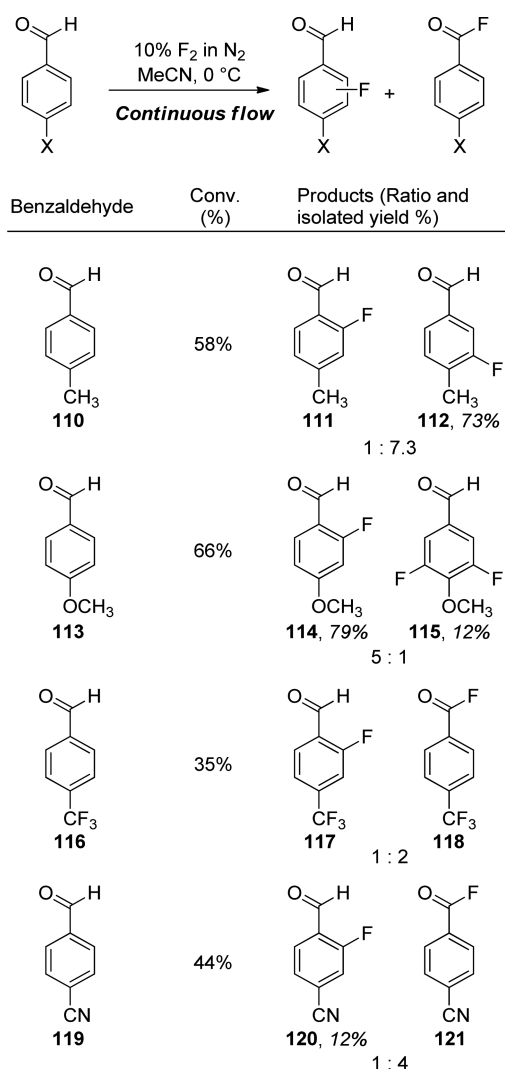
also demonstrated using the same setup with LDA, giving moderate to good yields (43–86% yields, 6 examples). Clogging issues were also observed despite the water quench

Scheme 23. Use of a FFMR for the Synthesis of 2,4,5-Trifluorobenzoic Acid (96) as a Continuous Process

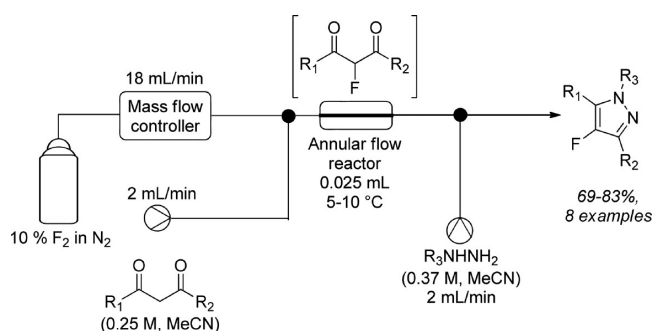




Scheme 25. Continuous Flow Fluorination of Benzaldehydes



Scheme 26. Two-Step Flow Synthesis of 4-Fluoro-3,5-dimethylpyrazole Derivatives through Direct Fluorination of 1,3-Dicarbonyl Substrates



but were overcome by changing to a dilution mixture of water and acetic acid (10:1).

The Jamison group has taken this approach a step further and shown the feasibility of quenching the intermediate lithium carboxylate with another organolithium to form unsymmetric ketones (Scheme 21).<sup>56</sup> Peristaltic pumps were used to pump the organolithium species (kept between 0 and 20 °C due to their instability) at a low concentration (0.1 M in THF) to

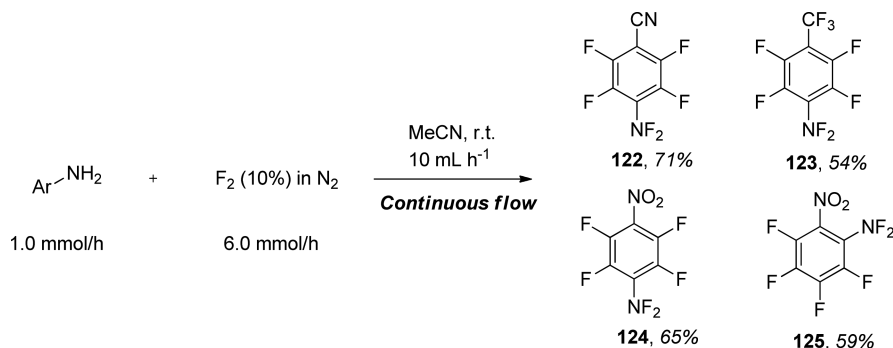
prevent issues of precipitation and potential reactor clogging. For some substrates, a degasser was used to remove the excess CO<sub>2</sub> before the organolithium quench to prevent symmetric ketone byproduct formation. The sequence was shown to be general for most substrates, giving good to excellent yields (40–92% yields, 18 examples).

Another interesting transformation also reported by the Jamison group involves the synthesis of cyclic carbonates through a bromine-catalyzed conversion of CO<sub>2</sub> and epoxides in continuous annular flow (Scheme 22).<sup>57</sup> A mixture of *N*-bromosuccinimide (NBS) and benzoyl peroxide (BPO) was used to form bromine, which activates the epoxide to nucleophilic attack. Substrates with aliphatic and aromatic substituents generally resulted in good to excellent yields (72–90% yields, 7 examples), with moderate yields being achieved for substrates with olefinic substituents (51–58% yields, 3 examples). Even though the authors postulate that the alkene pendant group might be interfering with the active catalyst, they do not report any bromination occurring on the alkene.

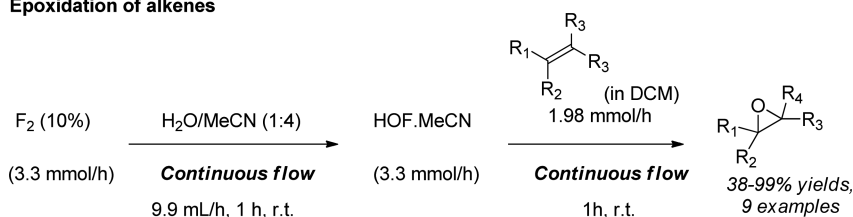
Recently, the continuous flow synthesis of 2,4,5-trifluorobenzoic acid (**96**) was reported through the Grignard reaction of 2,4,5-trifluorobromobenzene (**95**) and subsequent CO<sub>2</sub> trapping (Scheme 23) using a falling film microreactor (FFMR) (Figure 3).<sup>58</sup> The use of ethylmagnesium bromide as a Grignard exchange reagent was used due to the stability of the reagent, allowing the authors to conduct the reaction at 30 °C. As part of the study, the size of the T-mixer was investigated to avoid blockage of the system due to precipitation. An inner diameter of 1200 μm was found to be optimal, which prevents clogging and still allows for efficient mixing. Although the authors describe an efficient way of forming the carboxylic acid through this setup, the FFMR used has one drawback: the maximum flow rate is 0.83 mL/min and thus achieving high space–time yields is a challenge.

**The Use of Fluorine Gas in Flow.** Fluorine gas is a very corrosive and hazardous gas. To minimize working volumes and enhance safety, flow protocols for fluorine gas started as early as the 1990s. Three basic reactor designs have been used. The falling film microreactor was the first one to be explored by researchers at the Institut für Mikrotechnik (IMM) in Germany. IMM also developed a microbubble reactor for conducting direct fluorinations in flow. In addition, the Durham Fluorine Group has developed a continuous laminar flow reactor for fluorine-based reaction chemistries. All three reactors are very similar in design to other gas–liquid flow reactors shown above (Figures 2 and 3). However, certain required modifications in terms of the construction materials used for the main reactor as well as for seals and contacts need to be carefully considered for their resistance to fluorine gas or oxidation.<sup>59</sup>

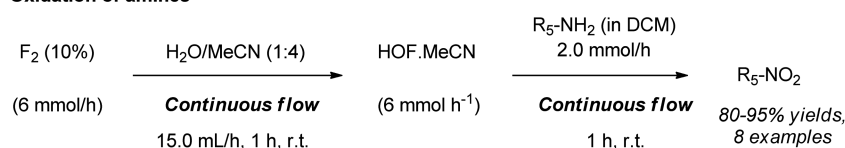
**Direct Fluorination of Organic Substrates.** Flow protocols employing fluorine gas have been developed under two main headings, principally for either selectively fluorinating organic substrates or performing oxidation reactions.<sup>59</sup> Within the former group, the electrophilic fluorination of aromatic systems is relatively well-represented in the literature. The substrate specificity varies widely from simple fluorination of toluene<sup>15,60</sup> to more advanced aromatic systems possessing several electron-donating groups where polyfluorination becomes an issue (Scheme 24).<sup>61</sup> Likewise, electron-deficient aromatics and heteroaromatics including several benzaldehyde derivatives have also been investigated (Scheme 25).<sup>62</sup>

Scheme 27. Continuous Flow Synthesis of *N,N*-Difluoroanilines Using Fluorine GasScheme 28. Use of *in Situ* Generated HOF·MeCN in Flow for the Epoxidation of Alkenes (Top) and Oxidation of Amines (Bottom)

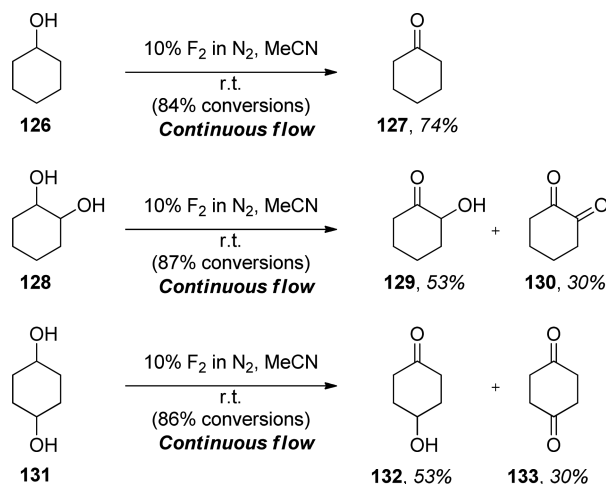
## Epoxidation of alkenes



## Oxidation of amines

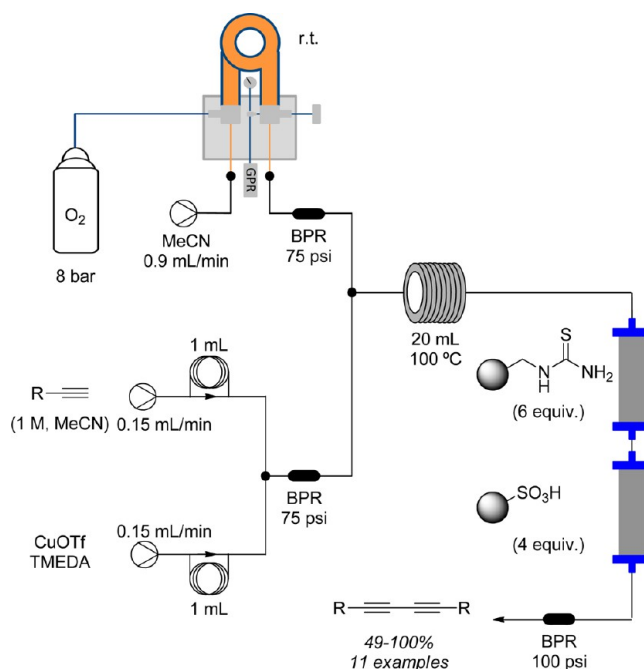


Scheme 29. Oxidation of Secondary Alcohols Using Fluorine Gas in Flow



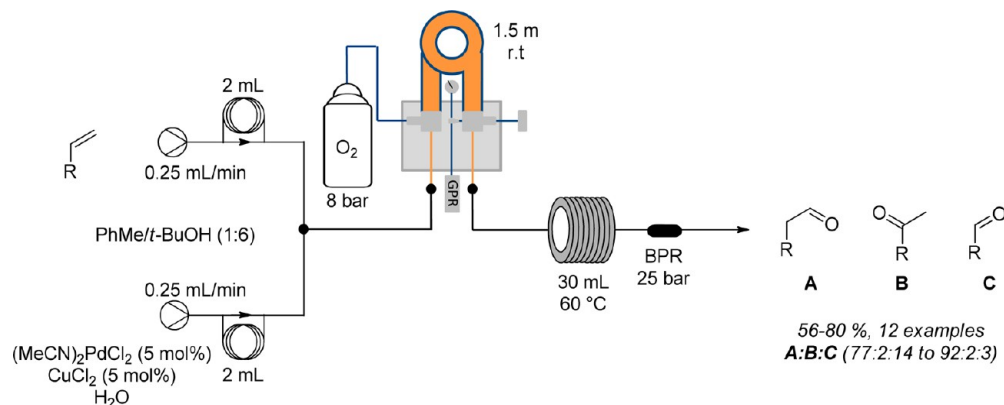
The continuous flow fluorination of 1,3-dicarbonyl systems is reported to proceed with good selectivities and in good to excellent yields (68–91%, 9 examples).<sup>62,63</sup> An investigation toward an industrial scale continuous flow fluorination of 1,3-dicarbonyl systems revealed that a productivity of 200 g/h could be reached with a commercial flow reactor.<sup>63c</sup> This methodology was applied to the formation of 4-fluoro-3,5-dimethylpyrazole derivatives from the corresponding mono-fluorinated 1,3-diketo compound via condensation with hydrazine derivatives (Scheme 26).<sup>63b</sup>

Scheme 30. Glaser–Hay Coupling in Continuous Flow Using Oxygen to Reoxidize the Copper Catalyst

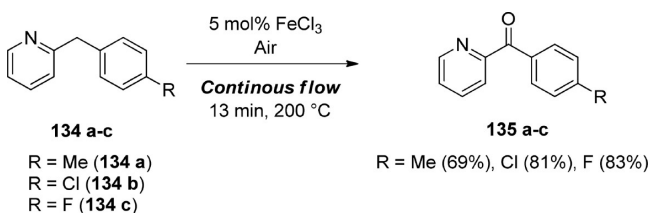


The continuous flow direct fluorination of various anilines has been reported by the Sandford group to yield the corresponding *N,N*-difluoroaniline products, which were highlighted as being versatile starting materials for additional

Scheme 31. Anti-Markovnikov Wacker Oxidation of Alkenes Using Oxygen in Flow



Scheme 32. Aerobic Oxidation of the 2-Benzylpyridine Derivatives to Their Corresponding 2-Benzoylpyridines in Flow



synthesis (Scheme 27).<sup>64</sup> A laminar flow reactor was used for these transformations to furnish the perfluoro products in moderate to good yields (54–71% yields, 4 examples). These were isolated in crude form after extraction with DCM and could be purified via silica chromatography. The authors remark that, even though similar compounds are sometimes unstable and potentially explosive, these isolated products were stable enough for the workup and purification procedure used, although they were still treated as potential explosives.

**Fluorine as an Oxidant.** The strong oxidizing power of fluorine can be utilized in oxidations. A mixture of fluorine, water, and acetonitrile rapidly forms the adduct HOF·MeCN, which is a strongly electrophilic oxygen transfer agent (Scheme 28). However, as this is not a very stable compound at room temperature, forming it in flow and directly consuming it is highly desirable. An *in situ* flow generation method was used for the epoxidation of several alkenes in moderate to excellent yields (38–99% yields, 9 examples).<sup>65</sup> Additionally, the

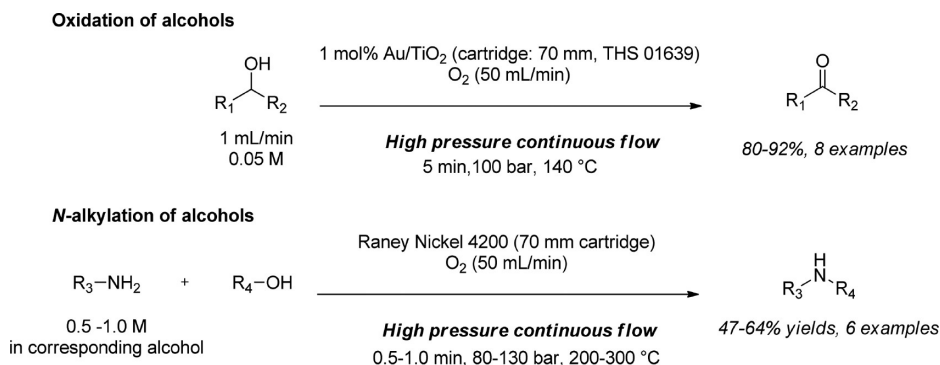
oxidation of various amines (80–95% yields, 8 examples) and anilines (51–95% yields, 13 examples) to the respective nitro groups was also disclosed.<sup>66</sup> The direct oxidation of alcohols was achieved by directly using fluorine as an oxidant without forming the HOF·MeCN adduct (Scheme 29).<sup>67</sup>

**The Use of Oxygen Gas in Flow.** With the recent move toward even more environmentally friendly and sustainable oxidation chemistry, metal oxidants like permanganate and chromium(VI) compounds are receiving less attention. Oxygen, however, is considered to be a good alternative either alone or in conjunction with various promoting catalysts.

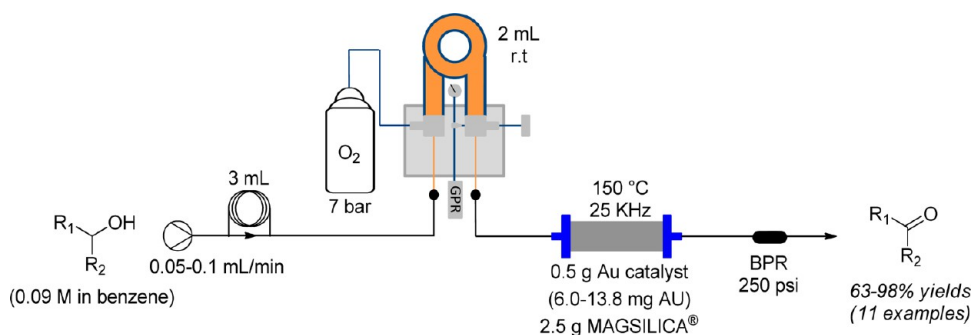
As an early example, the Glaser–Hay coupling in continuous flow was reported by the Ley group, with oxygen being used to reoxidize the copper catalyst.<sup>68</sup> A conventional tube-in-tube module was used to presaturate the solvent with oxygen, which was then mixed with an additional liquid substrate stream containing the copper(I) complex and the terminal alkyne (Scheme 30). A polymer-supported thiourea scavenger cartridge was used post-reaction to remove the copper catalyst from the flow stream, with an additional polymer-supported sulfonic acid cartridge to sequester the *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) base facilitating direct in-line purification. A range of aromatic and aliphatic terminal alkynes gave 1,3-butadiynes in moderate to excellent yields (49–100% yields, 11 examples).

Oxygen also has been used in continuous flow aerobic anti-Markovnikov Wacker oxidation.<sup>69</sup> Optimization of the reaction temperature, oxygen pressure, and water content was performed to achieve a good conversion and selectivity toward the desired aldehyde product. The reaction was successfully

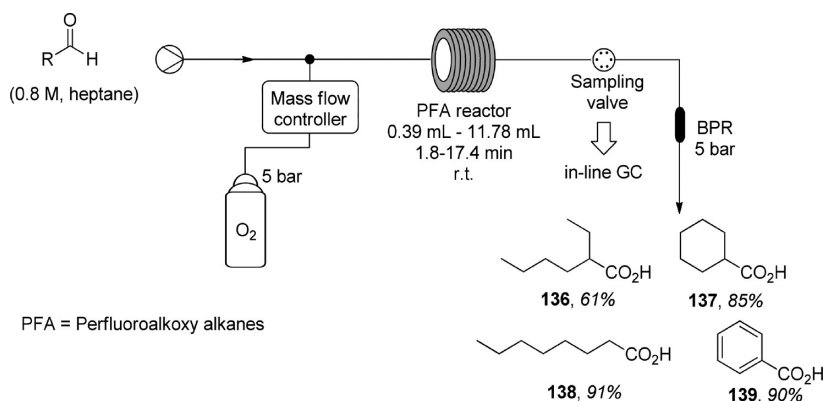
Scheme 33. Oxidation of Alcohols Using Oxygen in Flow (Top) and N-Alkylation of Alcohols Using Oxygen in Continuous Flow (Bottom)



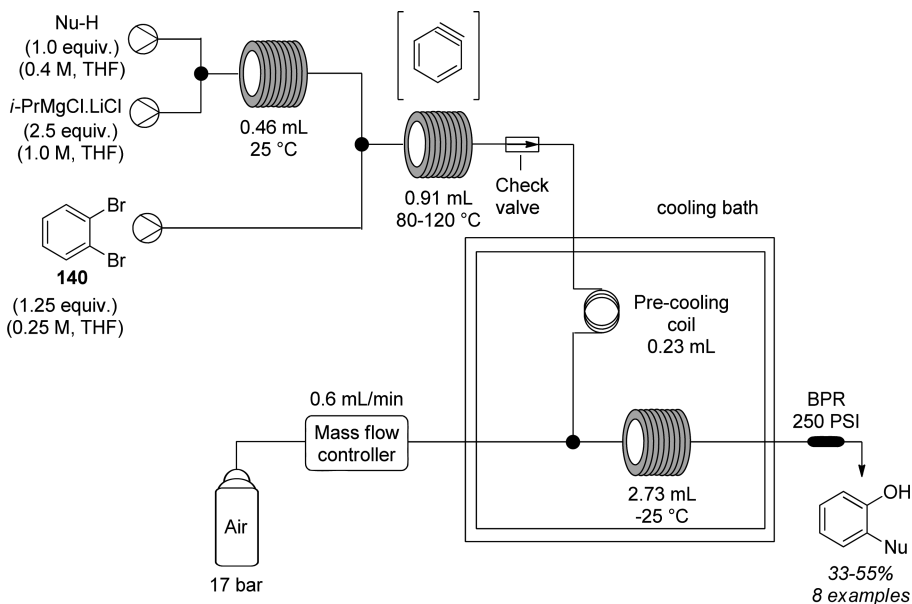
**Scheme 34. Oxidation of Allylic and Benzylic Alcohols Using Oxygen as the Oxidant and Gold-Doped Superparamagnetic Nanostructured Particles as Catalysts under Inductively Heated Flow Conditions**



**Scheme 35. Metal-Free Oxidation of Aldehydes To Form Carboxylic Acids Using Oxygen in Flow**



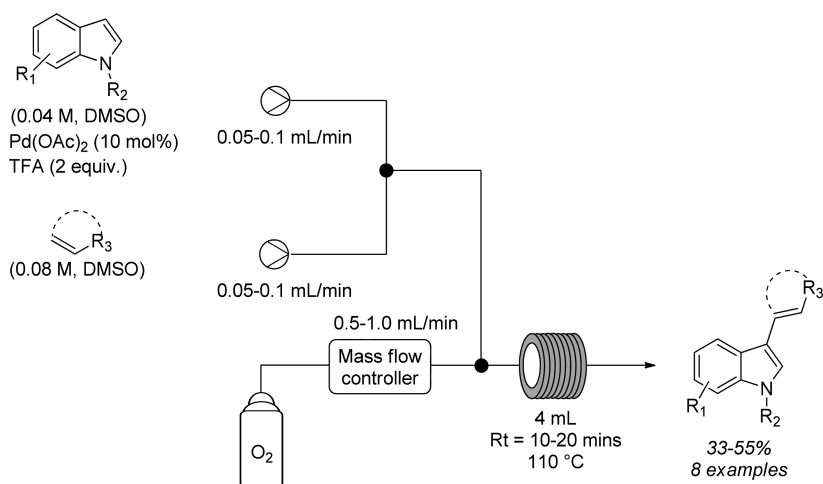
**Scheme 36. Integrated Flow System for the Synthesis of Ortho-Functionalized Phenols Using Air in Flow**



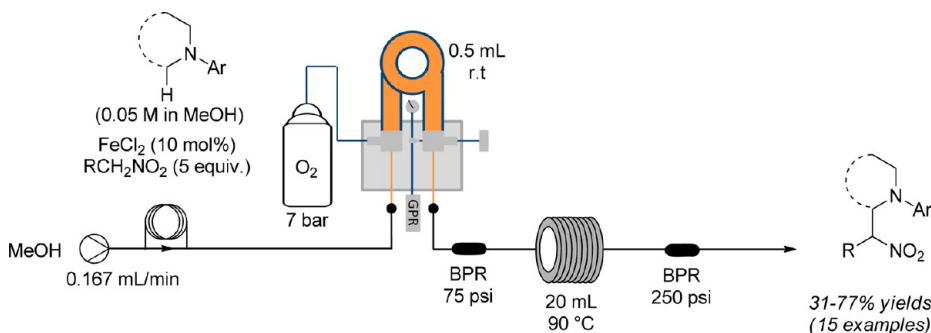
performed on a selection of styrenes possessing both electron-withdrawing as well as electron-donating groups in good yield (56–80%, 12 examples) and good to excellent selectivities (from 77:2:14 to 92:2:3 [A/B/C, Scheme 31]). Some further optimization on the setup was performed to demonstrate a scale-up of the reaction (96 mmol over 6 h) with the addition of an extra tube-in-tube reactor placed in series to achieve better oxidation of the copper catalyst (Scheme 31).

The air-promoted oxidation of 2-benzylpyridine derivatives to their corresponding 2-benzoylpyridines has been reported by the Kappe group, employing propylene carbonate as a solvent (Scheme 32).<sup>70</sup> A microreactor was used with oxygen (delivered as atmospheric air) added through a T-mixer to give plug flow, with the gas addition being supplied through a mass-flow controller. A high temperature (200 °C) and low residence time (13 min) combination was used to give the oxidation products in good yields (69–83% yields, 3 examples).

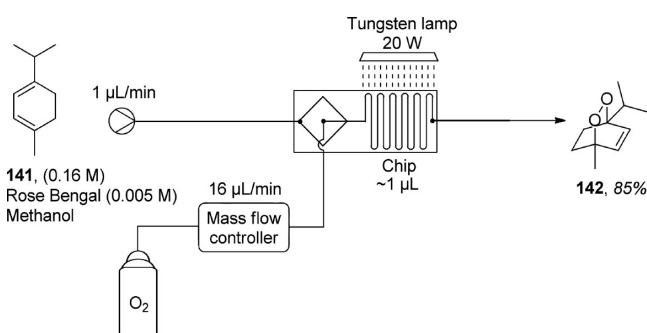
**Scheme 37. Pd(II)-Catalyzed Cross-Dehydrogenative Heck Reaction Using Oxygen Gas in Flow as an Oxidant to Reoxidize the Palladium Catalyst**



**Scheme 38. Iron-Catalyzed Aerobic Nitro-Mannich Reaction with Oxygen Gas as an Oxidant in Flow**

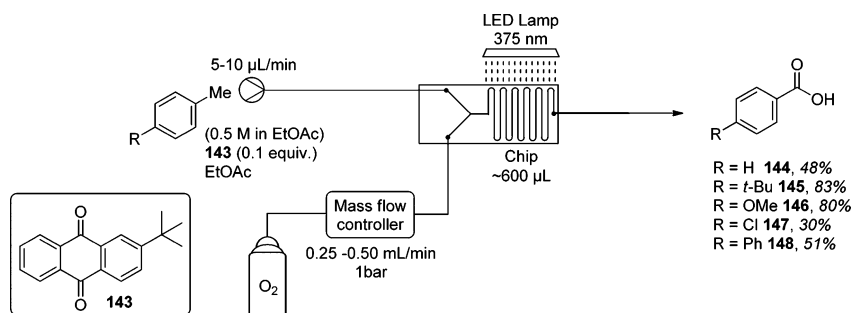


**Scheme 39. Microflow Preparation of Anthelmintic Ascaridole 142**



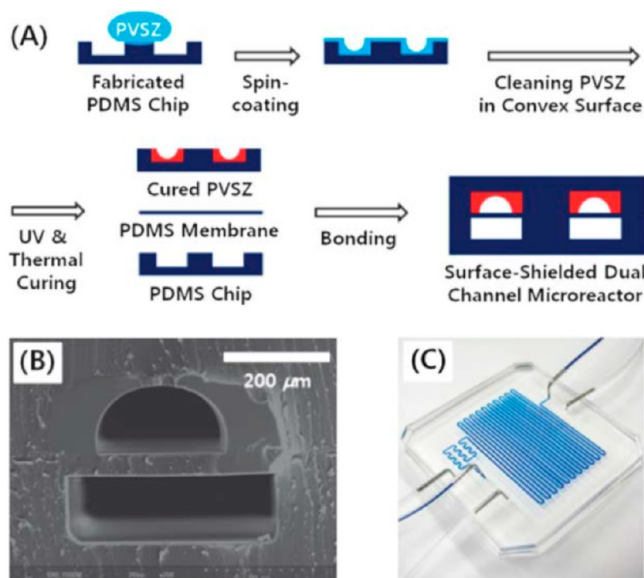
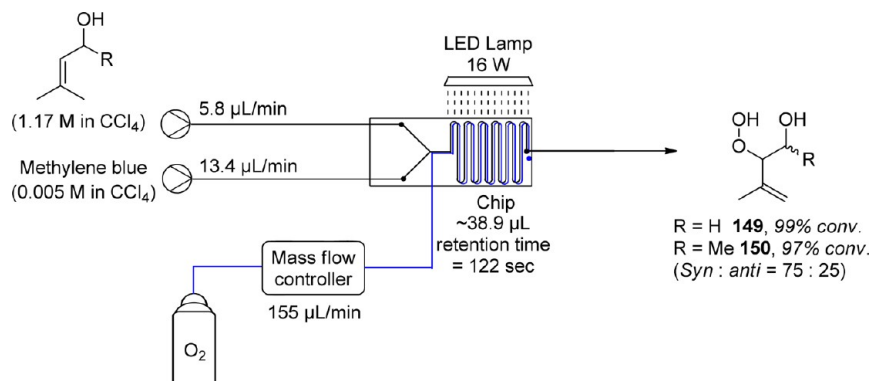
The Kocsis group have made use of the X-Cube to deliver oxygen for a number of industrial relevant oxidations and N-alkylation reactions (Scheme 33).<sup>71</sup> The oxidation of indoline and 1-phenylethanol were used for the optimization reactions in continuous flow, with a range of catalysts, oxidants, solvents, temperatures, and flow rates being evaluated. Subsequently, the derived conditions were used to convert a small collection of alcohol substrates to the corresponding ketones or aldehydes in good yields (80–92%, 8 examples). The optimization of the N-alkylation reaction using alcohols was performed in moderate yields (47–64% yields, 6 examples) employing activated Raney nickel as a catalyst for the oxidation of the alcohol in a “borrowing hydrogen” step. The intermediate imine formed, through the condensation of the amine and aldehyde, was then reduced by the borrowed hydrogen.

**Scheme 40. Photo-oxidation of 4-Substituted Toluene Derivatives Using Oxygen in Microflow**



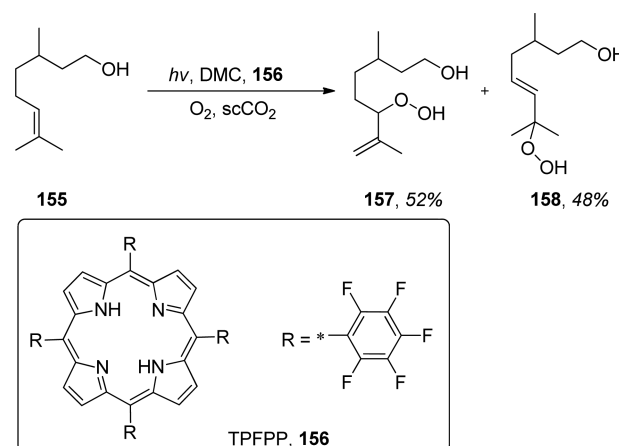


Scheme 41. Flow Photo-oxidation of Allylic Alcohols for the Synthesis of Artemisinin Using a PDMS Membrane Reactor



**Figure 7.** (A) Schematic illustration for the fabrication of a dual-channel microreactor with a poly(vinylsilazane) (PVSZ) shielded upper channel. (B) Cross-sectional view of dual microchannel with the PVSZ shielded upper channel. (C) The PVSZ shielded dual-channel microreactor filled with  $\text{O}_2$ , methylene blue (photosensitizer), and  $\alpha$ -terpinene (reagent). Reprinted with permission from ref 88. Copyright 2011 The Royal Society of Chemistry.

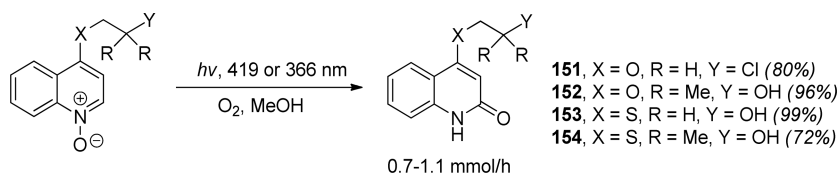
The Kirschning group have used oxygen gas delivered through a conventional tube-in-tube reactor to oxidize allylic and benzylic alcohols using gold-doped superparamagnetic nanostructured particles as the catalyst (Scheme 34).<sup>72</sup> The gold catalyst was immobilized on MAGSILICA, which facilitates inductive heating at medium frequency induction (25 kHz). Using this setup, no overoxidation was observed, which is encountered when the same process is conducted in batch.<sup>73</sup> Unfortunately, this setup worked best with benzene as the solvent, as other solvents such as methanol, ethyl acetate,

Scheme 43. Photo-oxidation of Citronellol in Flow Using  $\text{scCO}_2$ 

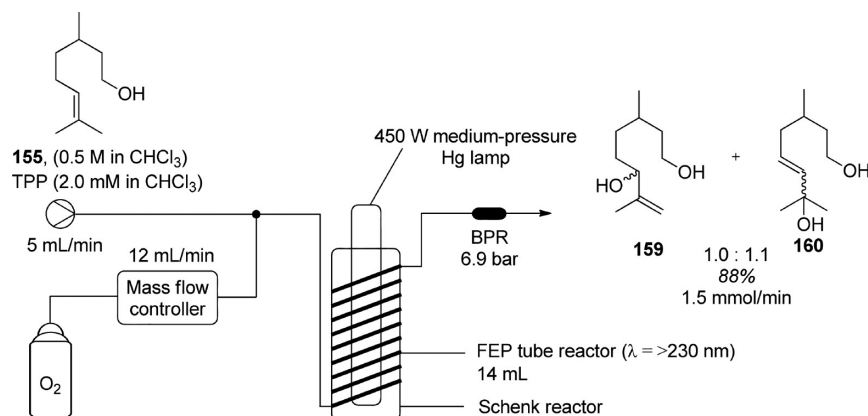
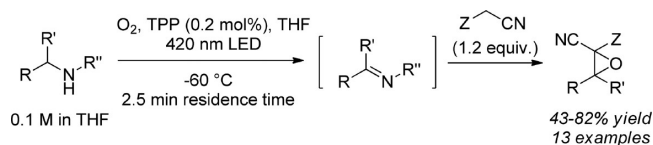
acetonitrile, and dichloromethane did not give full conversion. Toluene gave full conversions but produced byproducts derived from the oxidation of the methyl group, making the purification more difficult.

The continuous flow synthesis of carboxylic acids through the aerobic oxidation of aldehydes was reported by the Favre-Réguillon group using a plug flow approach (Scheme 35).<sup>74</sup> The process was run at ambient temperature with 5 bar of oxygen pressure without any added metal catalysts. This was claimed to cleanly (98% purity) generate the carboxylic acids in high yields (61–91% yields, 4 examples). The aerobic oxidation of the aldehydes goes through a free radical chain reaction to form the corresponding peracid, which reacts with the remaining aldehyde to produce a tetrahedral adduct (similar to the Criegee intermediate in the Baeyer–Villiger reaction). The tetrahedral adduct then rearranges, through a migration of hydrogen or alkyl group from the aldehyde, to give the corresponding carboxylate. The authors also described how, through the use of EPR spectroscopy and spin trap method-

Scheme 42. Photochemical Rearrangement of N-Oxides to Quinolones



Scheme 44. Photo-oxidation of Citronellol Using Oxygen in a Segmented Flow Regime

Scheme 45. Photo-oxidation of Amines for the Synthesis of  $\alpha$ -Cyanoepoxides

ology,<sup>75</sup> they could show that their process goes through a free radical auto-oxidation pathway that was initiated by a trace amount of overoxidized aldehyde present in the starting materials at ppm levels.

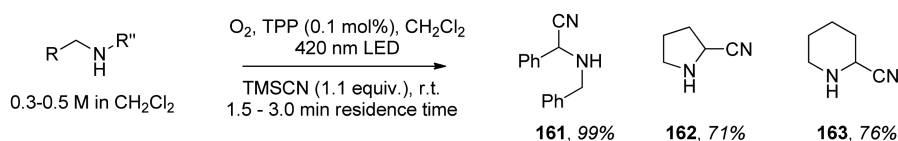
The synthesis of functionalized phenols using aerobic oxidation of Grignard substrates has been reported as a continuous flow procedure again using a plug flow system to deliver the oxygen.<sup>76</sup> The effect of temperature and system pressure were studied for the oxidation of phenylmagnesium bromide. Ultimately, a combination of 14 bar pressure and  $-25^{\circ}\text{C}$  was used to deliver a near quantitative conversion to the corresponding phenol in 3.4 min. These conditions were then applied to a wider range of Grignard reagents, with electron-rich systems forming the corresponding phenols in moderate to good yields (57–87%, 13 examples). The corresponding electron-deficient substrates required elevated temperatures ( $-10$  to  $25^{\circ}\text{C}$ ) but also gave comparable yields (53–81%). Some heteroaryl magnesium reagents were also tested, with thiophene and benzothiophene giving the ketone derivatives (24 and 32% yields, respectively). Other heteroaryl magnesium reagents gave the expected phenol products (47–86% yields, 3

examples). This transformation was also utilized for the preparation of ortho-functionalized phenols in an integrated three-step continuous process using compressed air instead of pure oxygen (Scheme 36). A number of substrates were prepared with a residence time of 14 min in combined yields of 33–55% for the 8 examples studied.

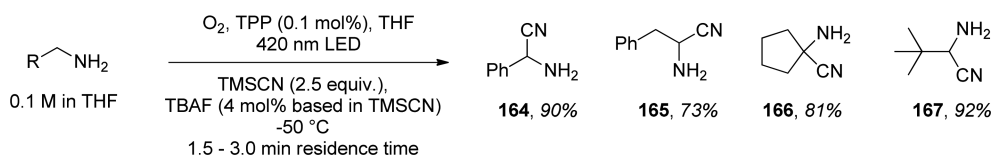
The C–H activation of indoles via a cross-dehydrogenative coupling was reported in a segmented flow reactor (Scheme 37).<sup>77</sup> The oxygen has a similar role as in the earlier example of the oxidative Heck reaction reported in a dual-channel microreactor.<sup>78</sup> During the optimization phase, the authors reported that better conversions were obtained when the reactor size was doubled and the flow rate was maintained rather than increasing the residence time by decreasing the flow rates. This was highlighted as being due to better mixing in the segmented flow path when higher flow rates were applied, ensuring efficient palladium reoxidation. Using optimized conditions, a number of vinyl indoles were synthesized in moderate to excellent yields (27–92%, 15 examples). The choice of solvent, DMSO, was based on the solubility of the palladium catalyst and its propensity to decrease palladium black formation, which could ultimately block the tubular reactor. Although it is practical at these small lab scales, the use of DMSO is not ideal for scale-up due to the difficulty of its removal, so this process would require reaction reengineering before being more widely applicable. Additionally, the authors did not mention any use of back-pressure regulators/pressure control, which would be essential to maintain a stabilized flow when scale up is required.

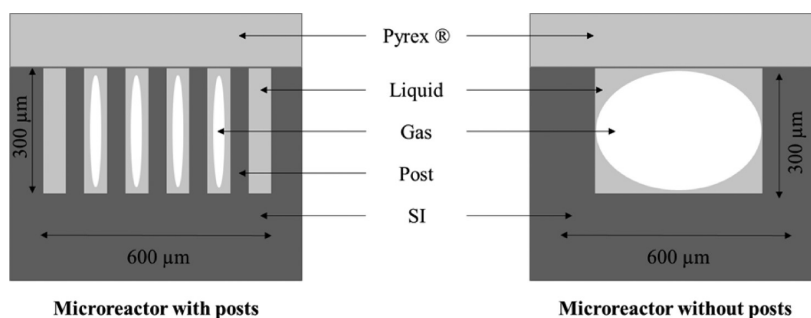
Scheme 46. Photo-oxidative Cyanation of Primary and Secondary Amines Using Singlet Oxygen

## Secondary amines



## Primary amines





**Figure 8.** Cross-section of the microreactor showing a comparison of reactor with posts and reactor without posts under multiphase flow.

An iron-catalyzed aerobic nitro-Mannich reaction was published by the Polyzos group that affords a direct  $\alpha$ -C(sp<sup>3</sup>)-H functionalization of N-aryl tetrahydroisoquinolines.<sup>79</sup> The oxygen was delivered through a conventional tube-in-tube reactor, with a stainless steel tube reactor being used as a residence time unit and to heat the flow stream (Scheme 38). A back-pressure regulator was placed just after the tube-in-tube reactor, which precludes in-line degassing. The reaction was quenched by dropping the liquid stream onto 2 equiv of triethylamine, which enabled isolation of the products in moderate to good yields after conventional purification (31–77%, 15 examples).

The biocatalytic production of catechols was demonstrated through a 2-hydroxybiphenyl 3-monooxygenase (HbpA) catalyzed conversion of 2-hydroxybiphenyl to 3-phenylcatechol using a conventional tube-in-tube to deliver an oxygen feed.<sup>80</sup> Although the authors showed a number of optimization steps to increase the gas transport into the solution, when the transformation was carried on an 80 mmol scale, only a 5% isolated yield was obtained, indicating that the enzyme catalyst employed was the limiting aspect of the process.

The use of oxygen in flow photochemistry has also been extensively reported.<sup>81</sup> The addition of singlet oxygen to  $\alpha$ -terpinene (**141**) to yield anthelmintic ascaridole (**142**) was realized using Rose Bengal as the sensitizer in a microchip reactor equipped with a 20 W tungsten lamp. The oxygen stream was introduced as a laminar flow (Scheme 39).<sup>82</sup> A direct comparison of the flow process with the batch process using a 500 W tungsten lamp shows a higher yield obtained for the flow process (85 vs 67%) but a lower productivity for the flow reactor (1.5 vs 175 mg/h). On the other hand, as the flow process should have a linear scalability, higher productivities could be achieved by multiple reactors in parallel rather than direct reactor scaling.

Recently, the photo-oxidation of 4-substituted toluene derivatives was described using a microchip reactor and oxygen delivered as a segmented flow using 2-*tert*-butylantraquinone (**143**) as a photosensitizer (Scheme 40).<sup>83</sup> Even though the yields obtained in flow were comparable to those in batch (30–83% yields), much shorter reaction times were needed: between 12 and 36 h were needed to achieve similar yields in batch.

The oxidation of (–)- $\beta$ -citronellol, using a borosilicate glass-loop microreactor with a diode array as a light source, was demonstrated in the synthesis of the fragrance rose oxide, with Rose Bengal as an oxygen sensitizer. However, the reaction time needed for reasonable conversion on a 1 mmol scale (400 min) was deemed to be too long for the reactor to be used for efficient scale up.<sup>84</sup>

The use of a TiO<sub>2</sub>-deposited photocatalyst within the channels of a flow microreactor has received attention for the oxidative degradation of *para*-chlorophenol,<sup>85</sup> toluene,<sup>85</sup> phenol,<sup>86</sup> and methylene blue.<sup>86</sup> Other synthetically useful transformations were also reported such as the oxidation of  $\alpha$ -terpinene (**141**) to yield ascaridole (**142**),<sup>87</sup> oxidation of L-methionine to the corresponding sulfoxide,<sup>87</sup> oxidation of  $\beta$ -citronellol,<sup>88</sup> and oxidation of allylic alcohols for the synthesis of the antimalarial artemisinin (Scheme 41).<sup>89</sup> The concept of this reactor is similar to that of the tube-in-tube reactors, but it employs a poly(dimethylsiloxane) (PDMS) membrane separating the two channels, allowing oxygen to permeate through the membrane and saturate the reaction mixture (Figure 7).

The photochemical rearrangements of an N-oxide moiety has been used for the synthesis of 4-substituted quinolone derivatives (Scheme 42).<sup>90</sup> Oxygen was used as a triplet quencher to suppress the [2 + 2] dimerization of the quinolones. This gave the desired quinolones (**151**–**154**) in good to excellent yields (72–99% yield, 4 examples), which were superior to the equivalent batch reactions. The flow reactor was built from a double coiled tubular reactor (Duran tube 7 mm; coil outer diameter: 75 mm; height: 200 mm; internal volume: 150 mL) placed in the middle of a Rayonet (RPR-100) photoreactor equipped with 16 lamps of fixed wavelength. The oxygen was bubbled through the solvent to presaturate the solution. The authors claimed that this approach could be used to deliver gram scale quantities of products. They also used the same setup for the synthesis of quinolones with tethered alkenes at the 4-position, which enabled subsequent intramolecular [2 + 2] cycloadditions.<sup>91</sup>

The high solubility of molecular oxygen in supercritical carbon dioxide (scCO<sub>2</sub>) has been exploited in the oxidation of citronellol (**155**) using 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPFPP, **156**) as a photosensitizer (Scheme 43).<sup>92</sup> Oxygen was delivered through a Rheodyne dosage unit and mixed with the scCO<sub>2</sub> before mixing with a solution of **155** in dimethyl carbonate (DMC) (1:1 v/v). The combined stream was then passed through a second micromixer before it was passed into a sapphire cell equipped with four 1000 lm LEDs. Complete consumption of **155** was achieved with 52% selectivity to **157** and 48% to **158** at a flow rate of 0.1 mL/min (1:1 v/v DMC/**155**), 1.0 mL/min of scCO<sub>2</sub>, and 2 equiv of O<sub>2</sub> at 180 bar. Although supercritical carbon dioxide was completely miscible with oxygen in all proportions used,<sup>93</sup> it is not the ideal solvent for most organic compounds, which can limit its use as a solvent for flow chemistry.<sup>94</sup>

The oxidation of citronellol has also been reported by the Seeberger group using oxygen in a segmented flow regime with tetraphenylporphyrin (TPP) as the photosensitizer.<sup>95</sup> In their setup (Scheme 44), the system could deliver up to 2.5 mmol/

Table 7. Ozonolysis of Triethyl Phosphite in Multichannel Reactors with and without Microfabricated Posts

microreactor	[P(OEt) <sub>3</sub> ] (mol/L)	O <sub>3</sub> /O <sub>2</sub> (%)	Q <sub>G</sub> (sccm) <sup>a</sup>	Q <sub>L</sub> (sccm) <sup>a</sup>	no. of ozone equiv	contact time (s)	conversion of reactant (%)	selectivity (%)
posts	0.247	5.6	2.5	0.05	0.51	1.25	48.1	95.1
posts	0.247	5.76	3.8	0.05	0.79	0.83	81.0	94.9
posts	0.247	5.87	4.7	0.05	1.00	0.67	97.0	98.1
posts	0.247	6.06	9.1	0.05	1.99	0.35	100.0	98.2
posts	0.247	5.96	9.3	0.10	1.00	0.34	100.0	98.7
no posts	0.244	6.02	1.3	0.0138	1.04	2.42	51.4	84.1
no posts	0.244	6.16	5.0	0.055	1.02	0.63	47.6	87.6
no posts	0.244	6.56	10.0	0.11	1.09	0.31	45.7	89.1
PTFE <sup>b</sup>	0.247	5.53	5.0	0.05	1.00	0.63	23.6	86.3

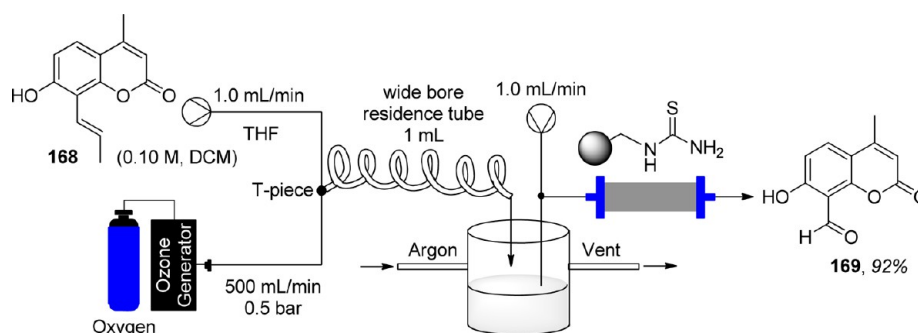
<sup>a</sup>sccm, cm<sup>3</sup>/min at standard conditions (273.15 K and 1 atm). Q<sub>G</sub>, gas flow rate; Q<sub>L</sub>, liquid (ethyl acetate) volumetric flow rate. <sup>b</sup>PTFE tubing 0.778 mm i.d. and 109 mm length (inner volume of microreactor with posts).

Table 8. Oxidation of Amine and Alkene with Multichannel Microreactor with Posts<sup>a</sup>

reactant	reactant concentration (mol/L)	O <sub>3</sub> /O <sub>2</sub> (%)	Q <sub>G</sub> (sccm) <sup>a</sup>	Q <sub>L</sub> (sccm) <sup>a</sup>	no. of ozone equiv	contact time (s)	conversion of reactant (%)	selectivity (%)
octylamine	0.105	6.16	10	0.088	2.99	0.32	98.7	79.7
1-decene	0.280	7.26	10	0.116	1.00	0.31	63.0	100.0
1-decene	0.280	7.39	10	0.0589	2.00	0.32	100.0	100.0
1-decene	0.280	6.63	10	0.035	2.99	0.32	100.0	100.0

<sup>a</sup>P(OEt)<sub>3</sub>/EtOAc was added from the quencher inlet for consumption of remaining ozone and reduction of ozonide to produce aldehyde.

Scheme 47. Flow Ozonolysis of Substrate 168 as Part of the Formation of 7-Hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde 169



min of product. The same setup was also used for the photo-oxidation of other substrates to show the scope of the method developed, including the flow synthesis of the antimalaria drug artemisinin.<sup>96</sup> A modified version of this setup using 420 nm LED lamps was subsequently applied to the transformation of amines to  $\alpha$ -cyanoepoxides through an oxygen-based oxidation (Scheme 45)<sup>97</sup> and the photo-oxidative cyanation of secondary amines to give 161–163 and primary amines to give 164–167 using singlet oxygen (Scheme 46).<sup>98</sup>

## THE APPLICATION OF OTHER GASES IN FLOW

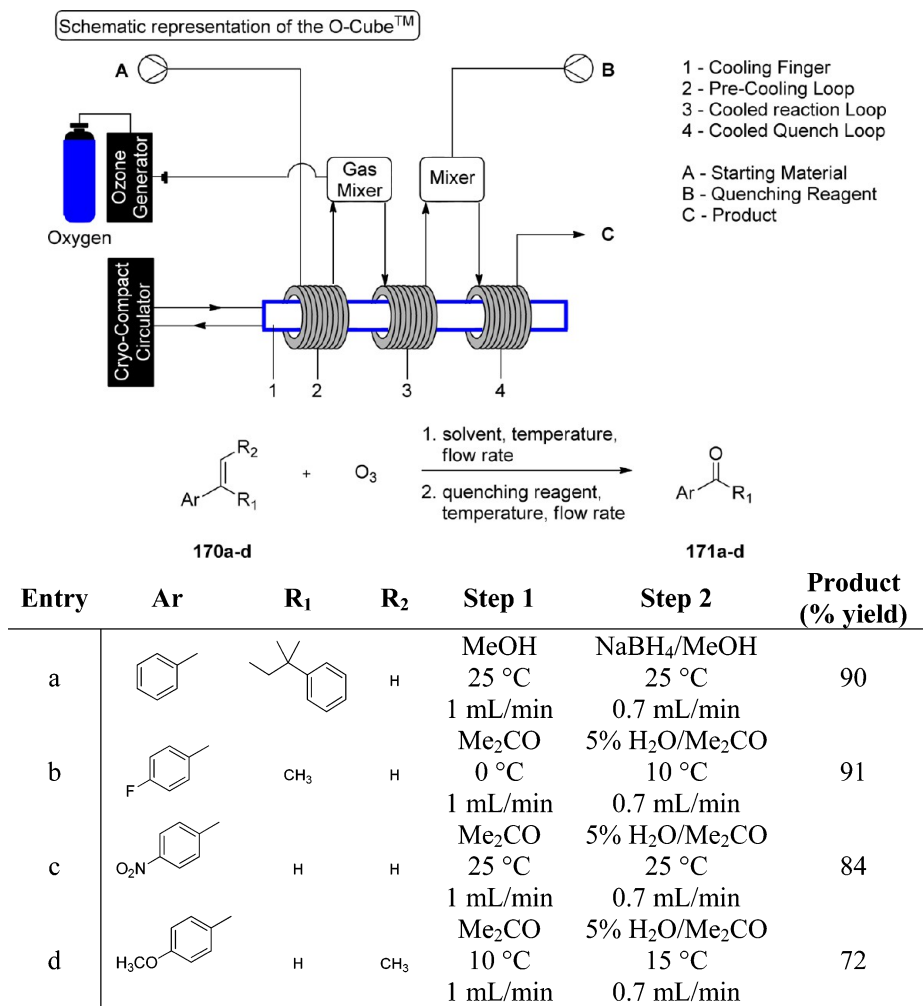
**The Use of Ozone in Flow.** Like carbon monoxide and hydrogen, ozone is a very reactive and thus hazardous gas. Nevertheless, it is very atom efficient and has a high oxidative potential similar to that of chlorine, making it useful for several transformations most commonly directed at the oxidative cleavage of alkenes. Flow chemistry offers a safer way for the use of ozone in the laboratory, which, if optimized properly, also can be used at larger scales. An early example showcasing the proof of principle for O<sub>3</sub> oxidation in flow was demonstrated by the Jensen group.<sup>99</sup> They described in detail how a multichannelled microreactor was built up with 48 pressure drop regions and 16 reaction channels, which ensures

a uniform distribution of gas and liquids throughout the channels. The ozone was generated through an electric discharge in a commercial ozonizer from 95% O<sub>2</sub> balanced with 5% N<sub>2</sub>. An annular flow was observed when the microreactor contained posts, whereas a slug flow regime was obtained with microreactors containing no posts (Figure 8). Even though the report primarily concentrates on the engineering of the multichannel microreactor and its physical properties, the group demonstrated ozonolysis by exploring three model reactions: the oxidation of triethyl phosphite (Table 7), octylamine, and 1-decene (Table 8).

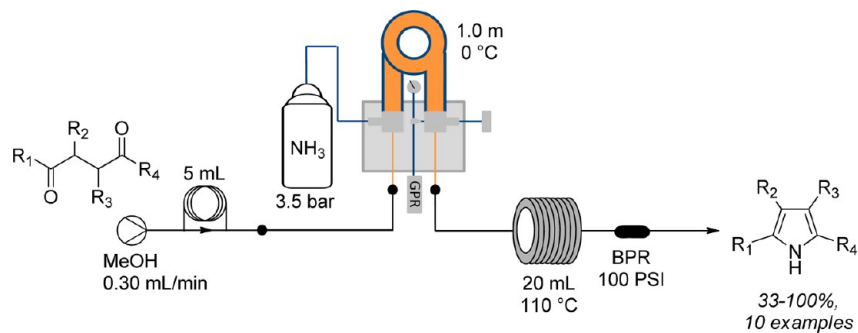
The use of a conventional tube-in-tube reactor for ozonolysis in flow was later reported by the Innovative Technology Centre (ITC).<sup>17b</sup> A basic solvent screen to evaluate solubility was first performed by following the kinetics and efficiency of ozone bleaching of Sudan-red 7B, with methanol showing the fastest rate of bleaching. A number of alkene substrates were subsequently oxidized in good to excellent yields (57–95% yields, 11 examples), showing the scope of this process in flow. To help with the purification process, the crude reaction mixture was immediately quenched using a polymer-supported triphenylphosphine reagent suspended in methanol. The same team also made use of flow ozonolysis as part of the synthesis of 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde



Table 9. Flow Ozonolysis Using the O-Cube



Scheme 48. Continuous flow Paal–Knorr Pyrrole Synthesis Using Gaseous Ammonia



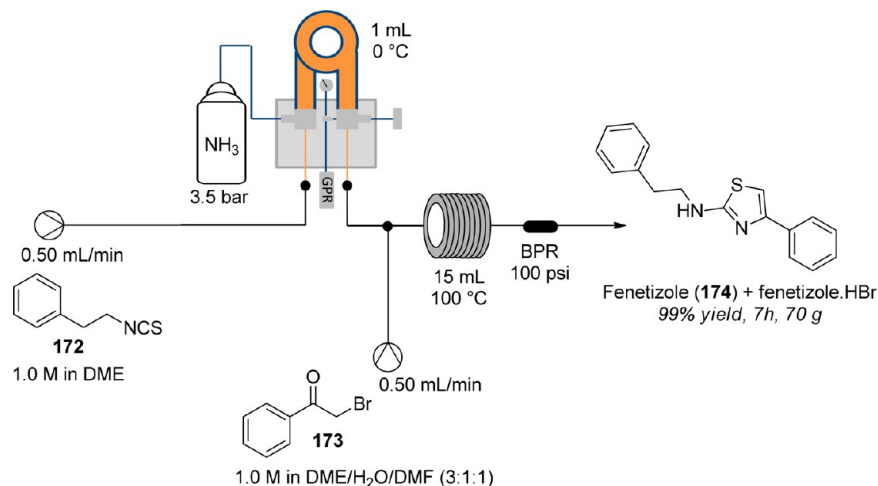
(169).<sup>100</sup> In this case, ozone was delivered through a T-mixer in a wavy-annular flow manner to a wide bore tube serving as a residence tube (Scheme 47). A similar system was also used as part of the flow-based synthesis of 2-aminoadamantane-2-carboxylic acid.<sup>101</sup>

The use of a commercial flow ozonolysis reactor, the O-Cube, was exemplified by the Kappe group (Table 9).<sup>102</sup> The reactor could be operated at temperatures of between  $-25\text{ }^{\circ}\text{C}$  and room temperature and at 0.2–2.0 mL/min flow rates. The instrument uses an  $\text{O}_2$  gas cylinder that is connected to an inbuilt  $\text{O}_3$  generator, with the  $\text{O}_2$  flow being supplied at a maximum flow rate of 20 mL/min. An internal analyzer

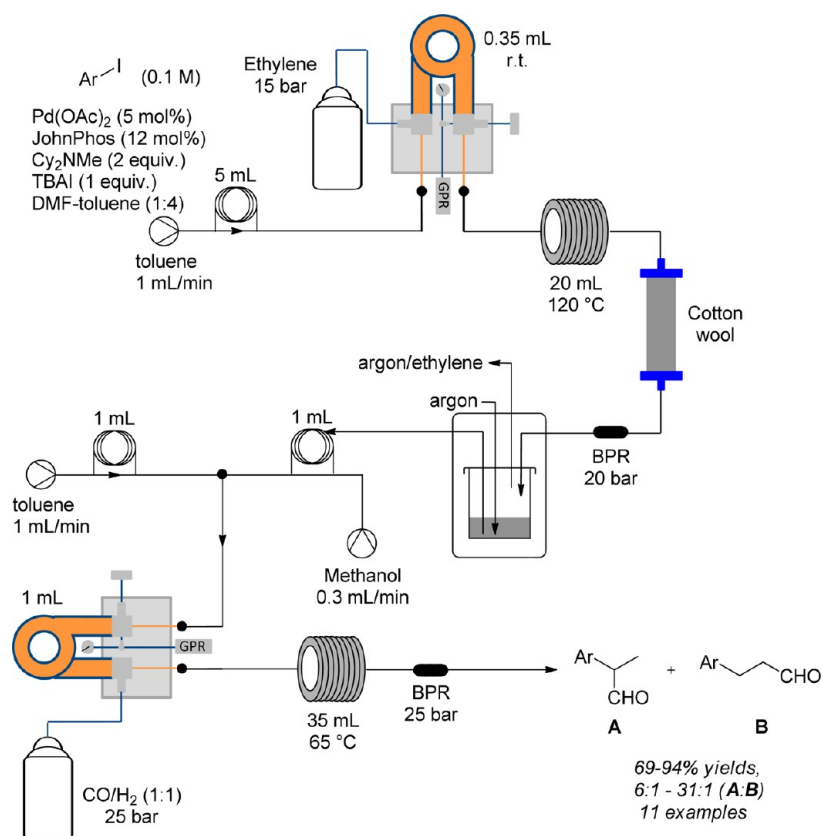
quantifies the O<sub>3</sub> generated, which is then mixed with the substrate stream. For optimum temperature control, the stream of substrate was continuously cooled before and after being mixed with O<sub>3</sub>. The ozonide formed is then quenched with a chemical quenching stream (i.e., triphenylphosphine), which is supplied via an independent pump to an in-line mixer. The ozonolysis of a number of styrene substrates was reported to give very good yields (72–91%, 4 examples). The authors also showed the ozonolysis of  $\beta$ -pinene in 70% yield, 1,1-diphenylprop-2-yn-1-ol in 86% yield, and octan-1-amine to give the corresponding nitroalkane in 73% yield.



Scheme 49. Continuous Flow Synthesis of Fenetizole Using Ammonia Gas



Scheme 50. Two-Step Telescoped Process for the Formation of Predominately Branched Aldehydes through a Rh-Catalyzed Hydroformylation of the Styrenes Using Ethylene and Syngas in Flow



The routine use of flow ozonolysis in industrial application is still in its infancy, but it is certainly due to receive greater attention as alternative oxidation systems involving heavy metals such as chromic acid and permanganate salts become even less acceptable options. Some steps toward scaled use of ozone have already been conducted. For example, Lonza has built a continuous flow process for ozonolysis of some of their intermediates that is capable of processing over 0.5 tonnes of product per day.<sup>103</sup> A setup for bench scale flow ozonolysis was also devised, which is an exact scale down of the plant system and uses a gas-liquid loop reactor equipped with a micro Venturi injector.

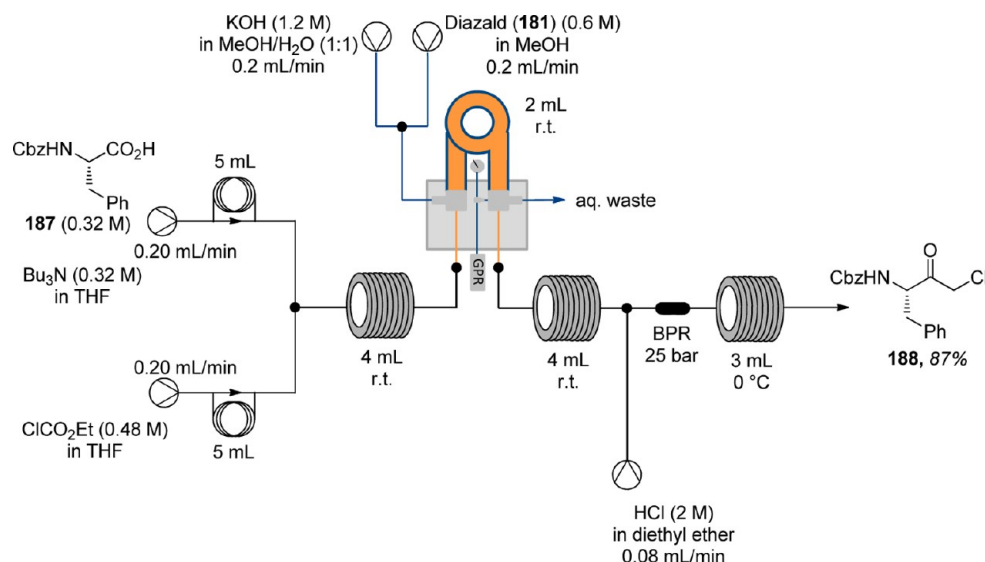
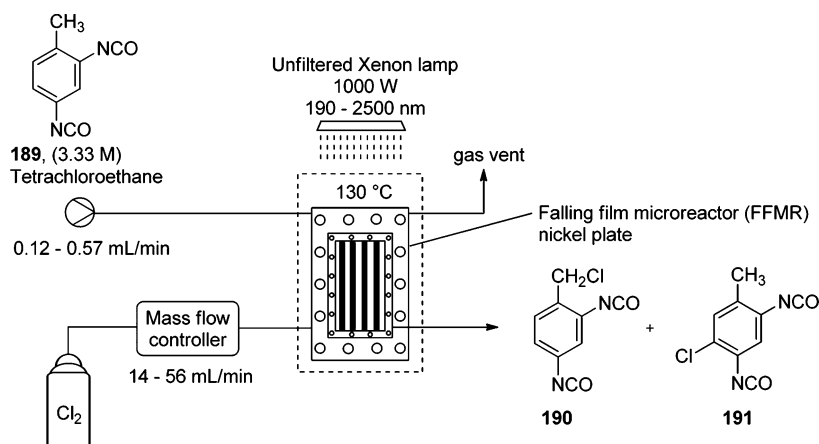
**The Use of Ammonia in Flow.** Paal-Knorr pyrrole synthesis using ammonia delivered through a conventional tube-in-tube module and reacting with 1,4-diketones was reported to proceed efficiently as a continuous flow process (Scheme 48).<sup>104</sup> The system was calibrated using an in-line titration of ammonia against bromocresol green as an indicator. This colorimetric indicator determined the ammonia concentration in the liquid flow and showed that a longer residence time and a lower temperature increases the ammonia concentration in the solvent. Additionally, an increase in ammonia concentration was observed when changing from dimethoxyethane to methanol as the reactor solvent.

The reaction scheme shows the conversion of compound **175** to products **176** and **177**. Compound **175** is (E)-2-(2-((1S,2S)-2-phenyl-2-(trimethylsilyl)ethyl)-2-oxocyclohex-1-en-1-yl)cyclohex-2-en-1-one, shown as a cyclohexenone with a side chain containing a cyclohexyl ring and a phenyl group. The reaction is performed in a flow system. Ethylene gas is bubbled through a 3 mL/min flow line. The main reaction mixture flows at 4 mL/min through a mass flow controller. The reaction is carried out in a 1.18 mL FEP tube reactor (λ > 230 nm) submerged in a quartz immersion well maintained at -78 °C. The reactor is irradiated by a 500 W high-pressure Hg lamp. The effluent passes through a BPR (back-pressure regulator) before being collected. The products are **176** (100% conversion, 52% d.e.) and **177** (a bicyclic derivative).

Entry	Substrate	Flow rate ( $\mu\text{L}/\text{min}$ )	KOH + Diazald flow rate ( $\mu\text{L}/\text{min}$ )	Product	Yield (%)	Daily output (mmol)
1		4	10		>99	2.88
2		1	4		>99	0.72
3		1	4		81	0.58
4		1	4		90	0.65

**The Use of Ethylene in Flow.** The palladium-catalyzed Mizoroki–Heck-type cross-coupling reaction of aryl iodides and ethylene gas for the formation of functionalized styrenes has been conducted as a continuous flow process.<sup>106</sup> The presence of the JohnPhos ligand and tetra-*n*-butylammonium iodide (TBAI) as an additive using 15 bar of ethylene led to the best conversions. Generally, good yields were obtained (43–85%, 10 examples), but substrates possessing an electron-withdrawing group gave lower yields. In addition, a small selection of aryl bromo substrates and heteroaryl iodides were tested, but, in general, these failed to give good yields under the standardized conditions.<sup>50b</sup> The method was used as part of the

**The Use of Chlorine Gas in Flow.** Chlorine gas is not normally encountered in many lab-based synthetic transformation due to its toxicity and strong oxidizing power. The use of chlorine in microflow allows for a safer way of using this dangerous gas in small quantities. The photochlorination of toluene-2,4-diisocyanate (**189**) has been demonstrated using a falling film microreactor (FFMR) (Figure 3).<sup>110</sup> The residence time was varied by changing the flow rate of the isocyanate **191** solution from 0.12 mL/min (equating to a residence time of 13.7 s) to 0.57 mL/min (4.8 s). As shown in Table 11, an increase in conversion from 30 to 81% was achieved at higher residence times, but a lower selectivity for the desired product

Scheme 52. Flow Synthesis of  $\alpha$ -Chloroketone Analogues Using *in Situ* Formed Diazomethane Delivered through a Tube-in-Tube ReactorTable 11. Photochlorination of Toluene-2,4-diisocyanate (**189**) in a FFMR at Various Flow Rates<sup>a</sup>

flow rate (mL/min)	conversion (%)	selectivity of <b>190</b> (%)	selectivity of <b>191</b> (%)	space-time yield <sup>b</sup> (mol/L/h)
0.12	81	67	5	321
0.23	55	80	5	401
0.38	41	79	8	393
0.57	30	79	12	398

<sup>a</sup>Thirty-two microchannels (600  $\mu\text{m} \times 300 \mu\text{m} \times 64 \mu\text{m}$ ). <sup>b</sup>Refers to the film volume in the microchannels.

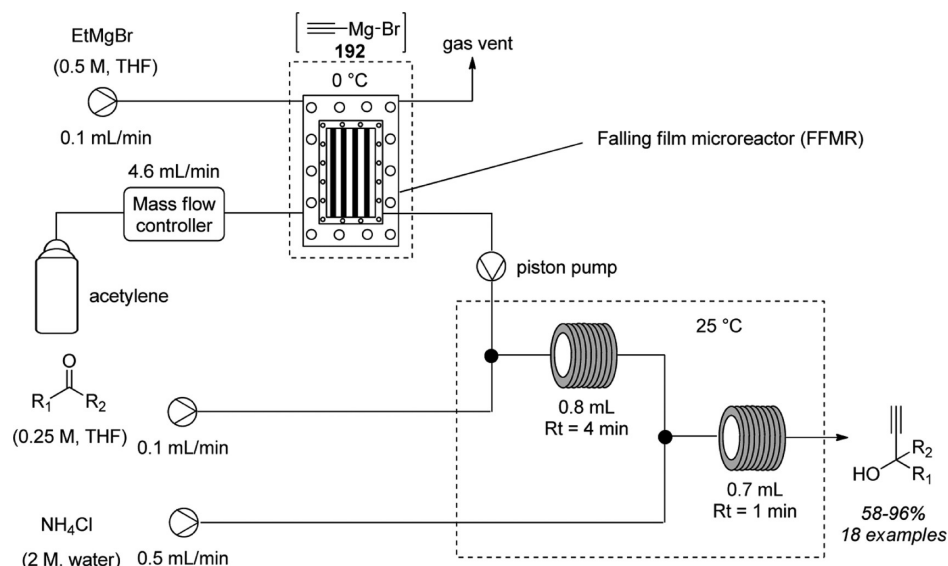
**190** was also observed (79 to 67% selectivity). The construction material for the FFMR was also studied. A microreactor made from iron instead of nickel was used to study the effect of a Lewis acid on the reaction ( $\text{FeCl}_3$  is formed by chlorination of the iron plate), with a drop in selectivity toward the desired product (**190**) occurring (50% selectivity at 80% conversion) when such a microreactor was used.

**The Use of Acetylene Gas in Flow.** The direct use of acetylene gas has been reported, to our knowledge, only by the Zhang group, in which they used it to prepare the ethynyl-Grignard reagent (**192**), which was further reacted with various carbonyls to form propargylic alcohols.<sup>111</sup> A FFMR was used, and after some optimization, the authors reported a set of conditions, overcoming noted precipitation issues, that gave the desired propargylic alcohols in excellent yields and selectivities (Scheme 53). The highest impact on selectivity came from

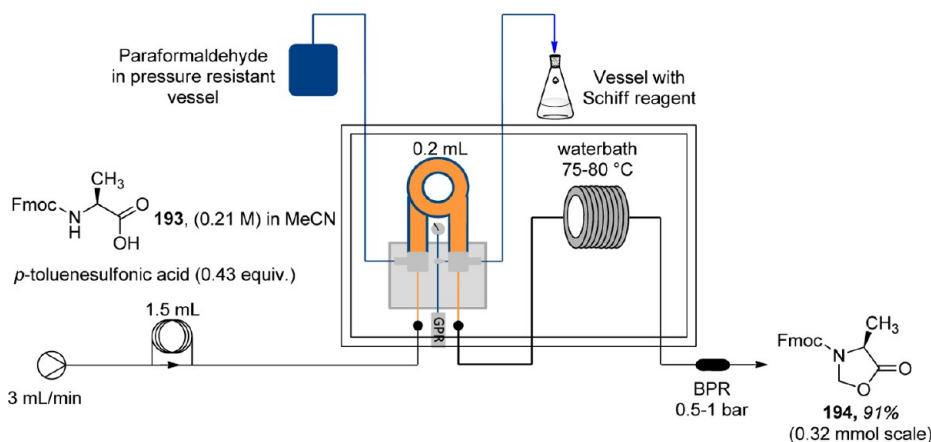
changing the flow rate, which was ascribed to the change in the thickness of the falling films, which improves the gas-liquid contact and mass transfer. A change in the molar ratio of  $\text{EtMgBr}$  and aldehyde from 1:1 to 2:1 improved the conversion from 57 to 100%. Ultimately, the optimized conditions were used to synthesis a number of propargylic alcohols that were obtained in excellent yields (87–96% yields, 17 examples), including an example that involved benzophenone, obtained in 58% yield.

**The Use of Formaldehyde in Flow.** Kunz and co-workers described the use of a conventional tube-in-tube reactor in the synthesis of N-methylamino acids (NMOs).<sup>112</sup> The two-step synthesis of NMOs, originally described by Freidinger et al., involves the formation of oxazolidinones that are then subjected to reduction conditions to achieve the ring-opening step to yield the desired NMO.<sup>113</sup> Using a pressure-resistant

Scheme 53. Synthesis of Propargylic Alcohol and Analogues in Microflow Using Acetylene Gas Delivered through a FFMR



Scheme 54. Flow Synthesis of Oxazolidinone (194) for the Formation of NMOs Using Formaldehyde in a Tube-in-Tube Reactor



vessel, paraformaldehyde was heated to form formaldehyde, which was passed through the tube-in-tube reactor for the formation of the oxazolidinone (Scheme 54). The Fmoc-alanine (193) and a catalytic amount of *p*-toluenesulfonic acid in acetonitrile were pumped through the reactor at 3 mL/h, with a back-pressure regulator of 1 atm needed to keep the formaldehyde from degassing. This afforded *N*-Fmoc-L-4-methyloxazolidin-5-one (194) in 91% yield. Even though the second step was also reported to be performed in flow, the two could not be telescoped in one continuous process, as the excess formaldehyde was found to quench the triethylsilane used in the ring-opening step. However, this could be potentially avoided if a subsequent tube-in-tube reactor under reduced pressure was to be applied after the first step to remove the excess formaldehyde from solution prior to it entering to the reductive step.

## CONCLUSIONS

The use of gases in continuous flow has increased access to several chemistries that were deemed to be either too dangerous to be conducted at large scales in batch chemistry or not efficient enough to be used due to the high pressure

requirements of the gases. Flow chemistry of gaseous reaction has not currently resulted in the invention of new chemistries but has rather made existing reactions more feasible. It has been shown that most of the synthetic gases (CO, CO<sub>2</sub>, O<sub>2</sub>, H<sub>2</sub>, C<sub>2</sub>H<sub>2</sub>, C<sub>2</sub>H<sub>4</sub>, CH<sub>2</sub>O, F<sub>2</sub>, O<sub>3</sub>, Cl<sub>2</sub>, CH<sub>2</sub>N<sub>2</sub> and NH<sub>3</sub>) can be employed in various flow reactors. Several new and now commercially available lab-based gas delivery modules have been described and exemplified. It appears that no one module can be used for all gas–liquid flow applications and that there is a requirement to select the best fit reactor for each specific use. For example, a tube-in-tube reactor and a segmented flow reactor tend to be more suitable if the reaction is scaled up to multigram–kilogram scale, whereas annular flow reactors and other microchip reactors are better suited for rapid small scale screening.

Even though a lot of gas–liquid transformations have been optimized to be used in continuous flow, we believe that there are still a large number of transformations yet to be tested. This will eventually lead to a shift into a greener, safer way of doing gas–liquid reactions, both in academia and ultimately in industrial settings.



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## Notes

The authors declare no competing financial interest.

## Biographies



Ian R. Baxendale obtained his Ph.D. under the supervision of Prof. Pavel Kocovsky at the University of Leicester investigating new organometallic catalysts based on group 6 transition metals for stereoselective allylic substitution reactions. He then moved to a postdoctoral position with Prof. Steven V. Ley at the University of Cambridge, initially conducting natural product synthesis before moving into the area of solid-supported reagents and scavengers. While in Cambridge, he was elected a Fellow and then Dean of Sidney Sussex College and also took over as the Head of Natural Science teaching. In 2003, he was awarded a Wolfson Royal Society Fellowship, which led to the co-founding in 2005 of the Innovative Technology Centre (ITC, Cambridge) as a centre of excellence for the study and development of advanced chemical synthesis tools and methodologies, where he was the Research Director. In 2008, he was promoted to Senior Research Associate in the Department of Chemistry and then in 2009 was awarded a Royal Society University Research Fellowship, becoming a member of the faculty. In 2012, he moved to Durham to take up the Chair of Synthetic Chemistry. His research interests are the design and implementation of new enabling technologies such as flow chemical synthesis (FCS), synthesis automation methodologies (SAM), microwave reactors, and immobilized reagents and scavengers to expedite complex chemical syntheses.



Carl J. Mallia attended the University of Malta, receiving a B.Sc. (Hons) degree in Chemistry and Biology in 2011 and a M.Sc. in Chemistry in 2012 working on the design and synthesis of intelligent molecules as lab-on-a-molecule (LOAM) systems for detecting disease conditions. He is currently reading for a Ph.D. at the University of Durham under the supervision of Prof. Ian R. Baxendale. His current research interests include flow synthesis using gases as reactants as well as new methodology toward the assembly of heterocyclic architectures relating to agrochemicals.

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